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THE DEVELOPMENT OF THE PLANTAR REFLEX IN CHILDREN *

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This research began as a study of general reflexes, but we soon found that the scope of such a problem was altogether too large and were forced to limit ourselves to the examination of the plantar reflex. We believe that we have shown three things: that the condition of the patient, particularly whether asleep or awake, is of considerable importance in the type of reaction obtained; that the type of stimulus and its strength are important, and that the reaction type varies considerably at various stages in the age development of the child.

REVIEW OF THE LITERATURE

Since Babinski first described what he chose to call "the phenomenon of the toes," in 1896, it has been an accepted fact that this reaction signified a disturbance of pyramidal tract function. His description of the reaction is complete in every detail and has been of tremendous value to neurologists. One phase of the plantar reaction which he did not discuss, but about which much has been written since, concerns the reaction in infants. Tournay [1] spoke of a similar phenomenon occurring in infants and stated that at the moment of birth the reaction is flexion, which is quickly replaced by extension. He also recorded the fact that such a reaction may occur at times in sleep, narcosis, epilepsy and strychnine poisoning. He considered that in central involvement the function of older mechanisms is liberated, while in lesions of the cord, for example, it may be due to some change in tone or chronaxia.

The variability of the reaction in infants can be compared with that in patients with lesions of the central nervous system. Babinski spoke of its presence in patients with normal tendon reflexs and again of its frequent absence in those with increased tendon reflexes and an ankle clonus.

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* Submitted for publication, Oct. 14, 1929.

* This paper is one of a series of studies on normal subjects from the University of Pennsylvania Graduate School of Medicine, under the direction of Dr. T. H. Weisenburg.

1. Tournay, M.: Encéphale **21**:718 (Nov.) 1926.

The age at which the plantar response assumes the adult type of reaction has been much discussed. Extension as a physiologic condition is usually accepted as being present in from 60 to 80 per cent of normal infants. DeBruin [2] found it in a large percentage of about 200 infants studied. The Vogts considered that the dorsal flexion which occurs before the fourth month shows fine athetotic movements which disappear after this period, although dorsal flexion still persists. Before the fourth month, it is termed a pseudo-Babinski sign; after the fourth month it resembles more closely the type of reaction seen in cases of lesions of the pyramidal tract. Minkowski [3] found dorsal flexion of the toes in fetuses of 3 or 4 months and believed that the reaction prevails until the second year. Zador [4] studied eighty infants ranging in age from 1 day to 14 months. He found dorsal flexion in 60 per cent up to 6 months, in 40 per cent from 6 to 9 months, but in only 5 per cent from 9 months on. He considered the reaction unlike the Babinski sign of adults and believed that in infants it represents a phylogenetically older type of reaction, which simulates the Babinski sign of adults because of lack of pyramidal tract development but is unlike it because of lack of certain inhibiting influences from the striatum. In this he agreed with the Vogts, who thought that the reaction became more typical at the fourth month, which is about the time that the striatum begins to assume its function.

The question of the relation of tone to dorsal flexion of the toes does not seem solved. According to Zador, a positive Babinski sign can be produced by small doses of scopolamine, which decreases tone. On the contrary, a positive Babinski sign can be abolished by a physiologic dose of physostigmine, which increases tone. In our cases, when dorsal flexion was present the tone of the extremity was usually increased except in the group of infants ranging in age from 4 days to 6 months, and in cases in which it was noted when the baby was asleep. A written communication from Dr. Kleitman states that he has also found reversal of the reaction of the great toe in the change from the sleeping to the waking states. He believes that the important thing is the behavior of the great toe, with little or no regard to the reaction of the other toes. In babies awake there was an almost constant attempt at some movement, which, of course, would have the effect of increasing tone.

Kino [5] stated that the plantar response, whether flexion or extension, is always greater in children and in older persons than in middle age.

2. De Bruin, M.: Nederl. Tijdschr v. Geneesk. **72**:3002, 1928.

3. Minkowski, M.: Schweiz. Arch. f. Neurol. u. Psychiat. **13**:475-514, 1923.

4. Zador, Julius: Monatschr. f. Psychiat. u. Neurol. **64**:336 (Aug.) 1927.

5. Kino, F.: Klin. Wchnschr., number 6, 1927.

He described a lack of reaction, or "stumme Sohle," as occurring only in cases of organic lesions, usually of moderate degree.

Schlesinger's [6] results in the main agreed with ours. He considered that the last change in type of reflex occurred sometime before the end of the first year. He spoke of occasional plantar flexion, extension of the great toe with flexion of the others, and of extension of all toes, with considerable variation in character. However, he stated that turning the head away at the time of taking the reflex diminishes it, while turning the head toward the side stimulated increases the reflex. Although we noted the same reaction occasionally, we do not believe it to be constant.

He also considered that plantar flexion prevails until the second month, and that dorsal flexion prevails from the second to the sixth month. He believed that these reactions were intimately concerned with the development of the extrapyramidal system control until myelinization of the pyramidal tracts. We agree with his conclusion that the changes in reaction depend on the development and control of the higher physiologic levels.

Wolpert [7] agreed with the Vogts that the extensor reaction in babies is not a true Babinski sign, but a pseudo-Babinski sign as a result of athetoid movement of the great toe. Schlesinger stated that the athetotic type of movement disappears at the end of the eighth month, and that the fetal Babinski sign disappears in from two to three months after the child begins to walk. On the contrary, we have found normal plantar flexor reactions in children who have neither walked nor attempted to walk.

METHODS OF STUDY AND INSTRUMENTS

The material for this study was derived from the maternity wards of the Philadelphia General Hospital, where babies from birth to 10 days of age were obtained, and from the Children's Hospital, St. Vincent's Home and the Child Hygiene Clinics of the city of Philadelphia, where babies were obtained for our 6 months and 12 months groups. In these groups, we used babies aged from 5 to 7 months and from 11 to 13 months.

In all we studied ten groups: a 1 day group of twenty-five cases; a 2 day group of twenty-five cases; a 3 day group of twenty-five cases, 4, 5 and 6 day groups of ten cases each; 7 and 10 day groups of twenty-five cases each, and 6 months and 1 year groups of twenty-six cases each. In addition, numerous children of intermediate ages were examined.

6. Schlesinger, Justus: Klin. Wchnschr. **6**:2384, 1927.

7. Wolpert, I.: Deutsche Ztschr. f. Nervenh. **89**:98-102, 1926.

In an attempt to determine the chronology of the plantar reflex and to learn if possible some of the factors involved in the control of the reaction, we studied a large series of infants ranging in age from 1 hour to 13 months.

This paper is limited strictly to a study of the plantar reflex. Although we made note of observations concerning other reflexes, a discussion of the other reflexes observed will not be included here. It has been said that the extensor reflex of the great toe in infants is definitely related to myelinization, and again that it has some definite relation to walking. The subject was approached with no preconceived ideas, with no attempt to prove or to disprove any theory but to gather a large number of facts, which we have attempted to analyze. As is frequently the case, impressions received early in the study were not borne out by a critical examination of the data collected.

The first problem was the selection of an instrument to be used as a stimulator. A key or match or some similar object was obviously out of the question because with such an instrument we could have no

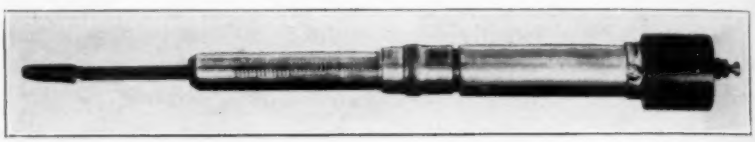

Fig. 1.—Stimulator devised by Dr. Grayson P. McCouch.

knowledge of the exact amount of pressure applied or of the length of the stimulus. It was deemed advisable to have the stimuli constant for each examination in order to rule out as much as possible the factor of the personal equation. With the assistance of Dr. Grayson McCouch [8] of the department of physiology of the Graduate School of Medicine, an instrument was made which was patterned after the von Frey hair but which had as the stimulator a wax point which would write on the skin. This was attached to a flat spring carried in an adjustable handle with a sleeve which could be used to shorten or lengthen the spring. Thus, with the sleeve at any given point, the strength of the stimulus must have constant value. The length of the stimulus could be measured after each stimulus by noting the length of the wax mark on the skin. The instrument was also designed in a way which made it possible to record electrically the duration of the stimulus in seconds. This portion of the device was not used in our work, since it seemed that the other checks made the stimuli sufficiently constant for our observation.

8. McCouch, G. P.: Am. J. Physiol. **71**:137 (Dec.) 1924.

In order to study more carefully the movements of the toes, motion pictures were made in certain selected cases by means of both regular speed and slow speed cameras. This proved to be of considerable value. We were thus able to note certain movements that had not been recorded by naked eye observation. Certain reactions were recorded in this way on films, but in all cases records were made in the chart form shown in the accompanying illustrations. All reactions that seemed of particular interest as well as other notes were recorded on each child's chart.

As far as possible, all the cases were studied in precisely the same manner. One of us made all the stimulations, at the same time observing the reactions, while the other also observed these reactions, charted them and occasionally made motion pictures of them. As many children as possible were studied both asleep and awake, but because of the type of material, it was impossible to study many of the older children while asleep. In all cases, the results recorded were obtained with the patient's head turned toward the side stimulated. In some cases, for purposes of comparison, the head was turned to the opposite side or was placed in an anteroposterior position, but since these positions consistently made no change in the reaction, the charts were made in all cases as already described in order to keep labyrinthine and neck reflexes a constant factor.

The routine of examination was as follows:

Each patient was studied first asleep if possible and then awake. The foot was divided into four quadrants which for purposes of description were called posterolateral, posteromedial, anterolateral and anteromedial. A number of stimuli were made in each quadrant alternately until the apparent true reaction was obtained; that is to say, in certain cases stimuli would produce variable or indefinite reactions, and in such cases the predominant movement of the toes would be charted. The results of stimuli of the 0 intensity were first obtained and charted; then a similar procedure was followed for the stronger, or what we chose to call the 30, stimulus. In the discussion of the results, however, unless otherwise specified, we refer to the 0 stimulus. All movements of all toes were charted either as flexion or as extension. From these movements we developed a number of terms for use in describing the results, such as flexion of all toes, flexion-extension of all toes, extension of all toes, extension-flexion of all toes and extension of the great toe with flexion and fanning of the other toes.

From the individual charts these observations were recorded on comprehensive charts—in groups according to age—and separated as to the strength of the stimulus, the condition of the baby, whether it was asleep or awake, and the quadrant stimulated. By thus tabulating our results, we were able to obtain percentages for the various reactions and thus to arrive at our conclusions.

RESULTS

In the 1, 2 and 3 day groups, the responses showed marked irregularity; at times we would get flexion, at times extension. For

purposes of tabulation and comparison, these three groups were put together as one large group of seventy-five children ranging in age from an hour or so to 72 hours. In this group, with the 0 stimulus, we found that extension is present in a much larger percentage of cases than flexion, while extension of the great toe with flexion of the other toes was found in a few more cases than was pure flexion. There was 61.7 per cent of pure extension, 18.6 per cent of flexion of the great toe with flexion of the others and 14.3 per cent of pure flexor reaction. This does not take into account the flexor-extension, the extensor-flexion and miscellaneous reactions. With the stronger or 30 stimulus, however, there is noted a marked change toward the flexor type of reaction. We find here only 39.6 per cent extensor reaction as compared to 61.7 per cent with the weaker stimulus. The percentages of the other reactions, except flexor, were not changed beyond the possibility of error, but the flexor reactions were more than doubled; i. e., 36 per cent with the stronger as compared to 14.3 per cent with the 0 stimulus.

Although the group of children studied during sleep was not as large as the group studied while awake, the ratio is reversed with the extensor response and with the extension response of the great toe with flexion of the other four, which gave 45.6 per cent with the 0 stimulus as compared to 34.1 per cent with the 30. Extension of the great toe with flexion of the other four showed 18.1 per cent with the 0 stimulus but only 10.6 per cent with the 30 stimulus. On the other hand, the flexor responses were greater with the 30 than with the 0; namely 47.9 per cent as compared to 32.7 per cent. In this group it is noted that extension-flexion accounted for a larger percentage of responses. By extension-flexion is meant a movement with two components, a beginning extensor component which is not complete followed by a flexor component which is complete.

In figure 2 the 4, 5 and 6 day groups were not charted because they seem to form an intermediate group in which the results, although tending toward those in the 7 day group, were nevertheless variable. Also, these groups were smaller and we thus cannot be sure of the results as in the larger groups. An analysis of these groups is presented in figure 2.

In the 7 day group the ratio of extensor responses to the 0 and the 30 stimuli remains the same, although extension occurs only a little more than half as frequently in this group as in the 1 to 3 day group. On the other hand, extension of the great toe with flexion of the other four is seen to be on the increase, with 43 per cent as compared to the earlier groups. With the stronger stimulus, however, extension of the great toe with flexion of the other four occurs at this age rather infrequently. With the 0 stimulus flexion occurs at about the same frequency

as in the earlier group, but with the stronger or 30 stimulus the number of flexor responses is much increased: 68 per cent as compared to 14 per cent with the lesser stimulus. The percentages in the indefinite groups remain more or less the same throughout the whole series.

In the 10 day groups with the 0 stimulus we find the highest percentage of extensor responses of any group; namely, 72 per cent in the babies who were awake. However, it will be noted that the same babies while asleep showed only 28 per cent extensor response. The

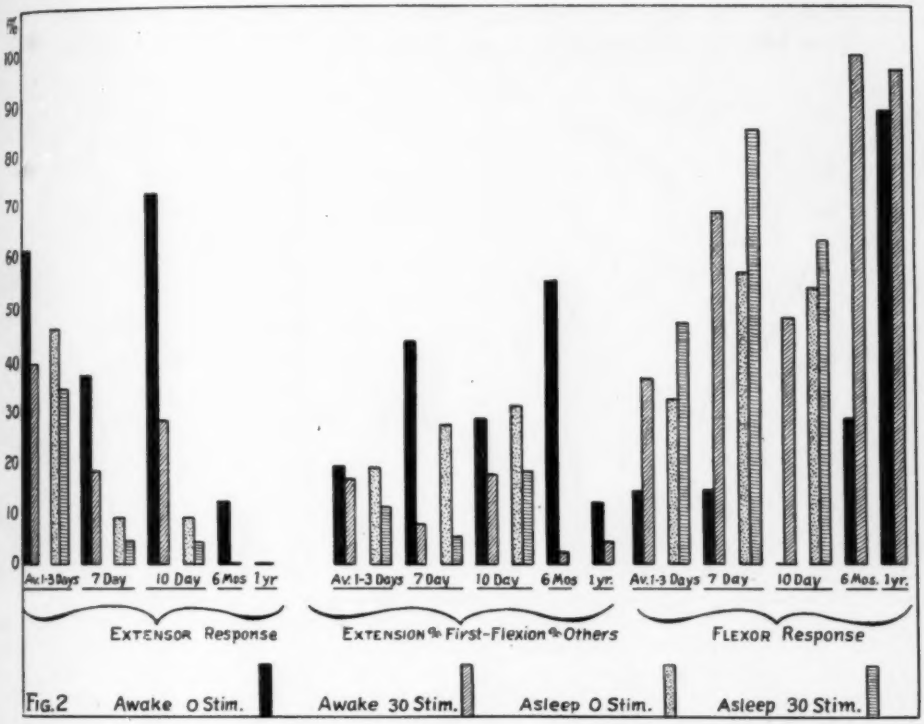

Fig. 2.—A comparison of the three main types of responses at various age levels, awake, asleep and with O and 30 stimuli. It will be noted that the extensor type of response tends to be much more prominent during the first ten days and the flexor response becomes prominent from then on.

remaining responses with the 0 stimulus were etxension of the great toe with flexion of the others in 28 per cent. Thus if we class the extensor response and extension of the great toe with flexion of the others in the same general group, we find at this age with the 0 stimulus a 100 per cent extensor type of reaction. The 30 stimulus gave extension of the great toe with flexion of the others in 17 per cent of the babies who were awake and in 17.3 per cent of those asleep, whereas

with the lighter stimulus the percentage of extension of the great toe with flexion of the others was slightly greater in the group asleep than in the group awake. An interesting observation in this group was the absence of any flexor responses with the 0 stimulus with the babies awake; with the babies asleep, and the same stimulus, there was 53.9 per cent flexion. With the 30 stimulus there was 43 per cent flexor response in the group awake and 67.3 per cent in the group asleep.

None of the babies in the 6 months or 1 year group were studied while asleep. In the 6 months group we find the greatest percentage of extension of the great toe with flexion of the others of any group. Thus with the 0 stimulus there was 60 per cent of this type of reaction,

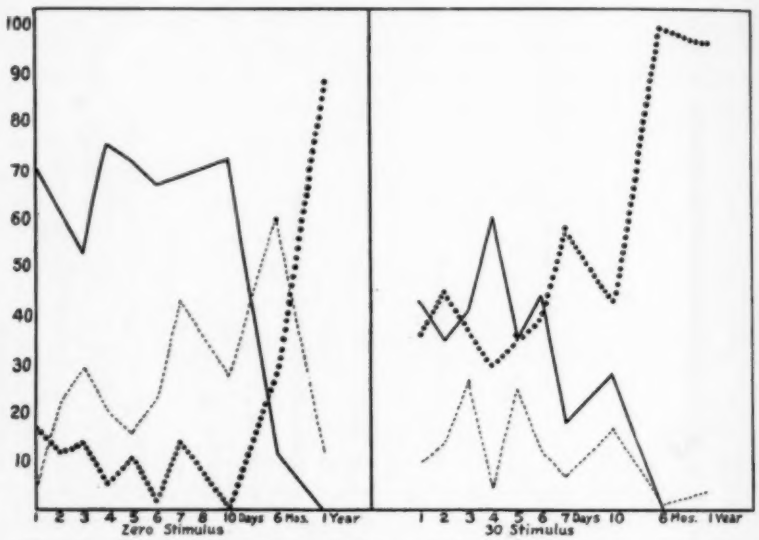

Fig. 3.—A comparison in graph form of the response in percentage by days with the subject awake (solid line). Again will be noted the prominence of the extensor response up to 10 days (light dotted line), with the increase of the flexor response from that period (heavy dotted line).

with 12 per cent extensor and 28 per cent flexor reactions. But with the stronger stimulus the reactions were practically all flexor, 99 per cent, with no extensor response to the stronger stimulus. In the 1 year group we found no extensor responses with either the 0 or the 30 stimulus. In this group, 12 per cent of the responses consisted of extension of the great toe with flexion of the others with the 0 stimulus and 4 per cent with the 30 stimulus. It will be noted that there were no indefinite responses in the 6 months or 1 year group.

By taking these results and putting them in graph form, charting the percentage of responses as ordinates and the age of the infants as abscissae, one can plot a fairly regular curve. All responses show con-

siderable variability; in the main, however, extensor responses with the 0 stimulus are at the highest level at the ages of from 4 to 10 days and at 1 year have completely disappeared. The extension of the great toe with flexion of the others shows a gradual progression upward, reaching its highest level at 6 months and almost disappearing in the

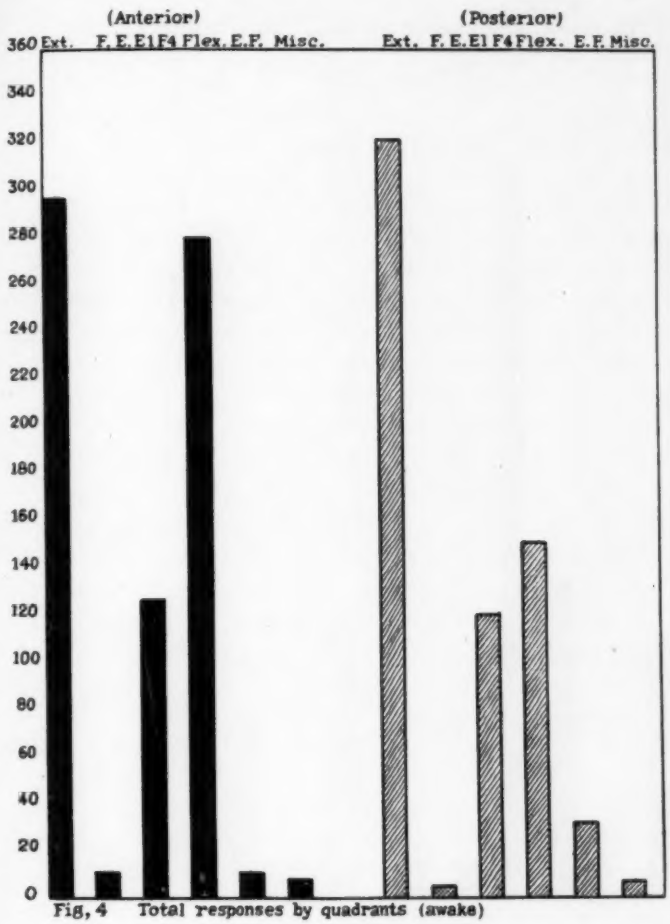

Fig. 4.—A comparison of the total number of responses by quadrants with the subject awake. It will be noted that the extensor reactions are more prominent in the posterior quadrant while the flexor are comparatively more prominent in the anterior quadrants.

1 year group. Again, flexion is variable, being at its lowest point at 10 days and at the highest level in the oldest group. With the greater strength of stimulus, however, a different situation obtains, flexor responses being much more prominent than with the weaker stimulus.

Here one finds extension at its highest point in the 4 day group and more or less regularly diminishing to the 6 months group, where it disappears and is also absent in the 1 year group. The Babinski reaction is variable, reaching its highest point at 3 and 5 days and alternating with extension at 4 days. At 6 months and 1 year it has almost dis-

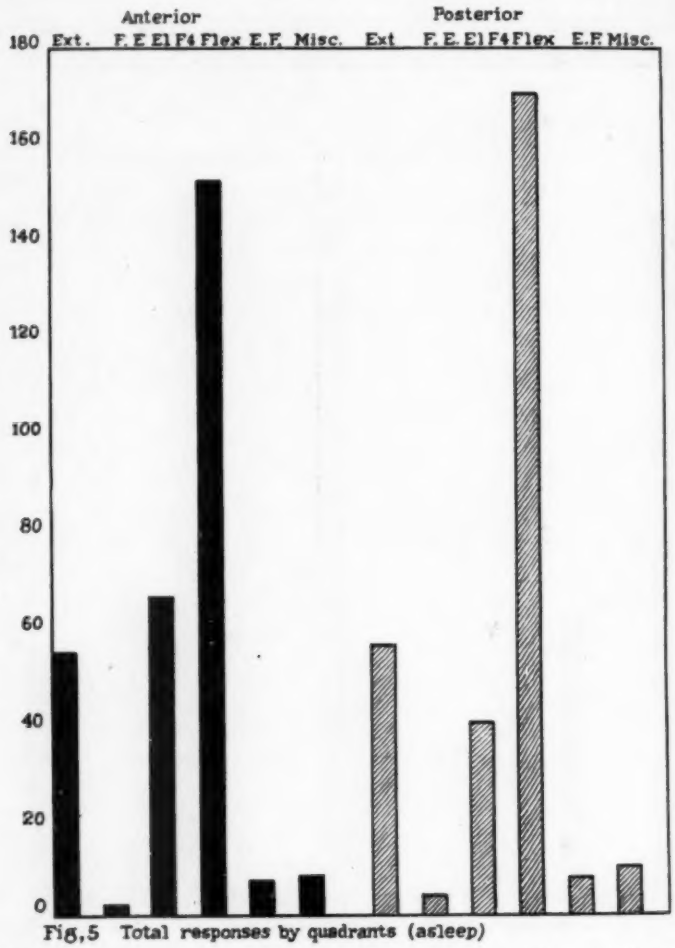

Fig. 5.—A comparison of the total responses by quadrants with the subject asleep. The flexor responses here are much more prominent than the extensor, both in the anterior and in the posterior quadrants.

appeared. Flexor responses, however, are almost constant, showing only moderate variability during the first ten days but at the same time comparing favorably with extension and far outnumbering the Babinski responses. In 6 months and 1 year groups, flexion is by far the predominant response to the 30 stimulus.

In an analysis of the results, with a comparison of the total responses awake and asleep, we find that in the 1 day group there are more extensor responses in the group asleep than in the groups awake. However, after the first day we find that extension is much more predominant when the child is awake than when it is asleep. By the same token, flexion is much more predominant when the baby is asleep. On the other hand, the extension of the great toe with flexion of the others is extremely variable, being comparatively the same in the first 3 day groups, while in the 4 day it occurred nearly twice as many times with the baby asleep. In contrast to this, in the 5 day group it was found ten times as frequently in the infants who were awake. The 6 day group compared favorably with the 4 day, while the 7 day infants, when awake, showed twice as many extensions of the great toe with flexion of the others as when asleep. In the 10 day group, again, the responses were nearly equal. It is unfortunate that we were unable to examine a large series asleep in the 6 months and 12 months groups. It will be noted, however, that in the same baby with the conditions constant except that the child is asleep or awake, the flexor responses show a marked tendency to increase when the child is asleep. This rule holds strictly true with the exception of the 1 day group.

In comparing the total responses by quadrants with the infants awake it will be seen that flexion compares rather well with extension, having only a slight lead in the anterior quadrants of the foot. However, in the posterior quadrants there were more than twice as many extensor responses as flexor. A more important observation, however, is that the number of responses by extension of the great toe with flexion of the others is essentially the same in the two halves of the foot. This observation does not hold true when the infants are examined while asleep. The anterior and posterior halves of the foot are about even, and in both cases we found about three times as many flexor responses as extensor. This bears out our previous assumption that flexion responses occur more frequently if the subject is asleep. Again the extension response of the great toe with flexion of the others was about equal in the two halves of the foot.

COMMENT

The value of this study does not seem limited only to the question of when the normal plantar reflex should be extensor, flexor or Babinski in type and the relation of such reflexes to the development of the nervous system, but applies also to the technic of taking the plantar reflex, and the condition of the patient. The clinical value derived possibly does not concern those patients who have a positive Babinski reaction with any sort of stimulus but does concern those

patients in whom the plantar responses are indefinite, vague or variable. In such cases the final decision as to the type of response obtained and its meaning has been perhaps the result of experience, but also in our conception may be aided by a study of this sort.

The question of the relation of myelinization to the development of function has long been a debatable one. Thus it is known that a Babinski response to plantar stimulation in an adult almost invariably means interference with the function of the pyramidal tract. In the infant a plantar response of this type has been considered normal up to a certain age—i. e., the age of myelinization of the pyramidal tracts—or even, by some observers, the age at which the child begins to walk. These conclusions do not find confirmation in our work. Several children examined, who came just at the lowest level of our highest age group and who had never walked but who were apparently physically normal, were found to have a complete and typical flexor response. During the first few days of life, plantar responses are extremely variable, but there are flexor responses in a large number of cases; as a matter of fact, for the first three of four days the flexor responses outnumber those of extension of the great toe with flexion of the others, although there are a greater number of complete extensor than of complete flexor responses at this period. At 6 months the pure flexor responses outnumber the pure extensor responses, but the percentage of reactions of extension of the great toe with flexion of the others is greatest at this period. At 1 year, both extensor types of reaction have nearly disappeared, to be replaced by pure flexion. The significance of the extensor response of all toes may have a meaning similar to that of the extension response of the great toe with reflexion and fanning of the others, or again, it may not. At any rate, it is present throughout the series in a larger number than is the latter type of response.

A point which we consider deserves attention and for which we have no adequate explanation is the fairly high incidence of flexor responses during the first two or three days, which are then replaced by pure extensor responses or responses with extension of the great toe and flexion of the others, only to reappear sometime between the ages of 6 months and 1 year. We know that such a change does occur in a given case since we have studied individual children who showed first flexion and later pure extension, or extension of the great toe with flexion of the others. Unfortunately, we were not able to carry these cases through to our age limits, but because of the relative infrequency of extensor reactions at the age of 1 year it is safe to assume that in these cases a flexor reaction would have again developed. Is this change of reaction to precisely the same type of stimulus due to changes in the relative chronaxia of the flexors and extensors as suggested by

Bourguignon? One would hardly expect such a rapid reversal of chronaxia in the first few days of the child's life. Bourguignon stated that at birth there is a heterochronism of the sensory and motor nerves which is gradually replaced by isochronism. This heterochronism is said to disappear at from 15 to 18 months. This, however, does not explain a reversal of reaction such as apparently takes place after the first few days of the child's life. In another contribution, Bourguignon stated that normally (in adults with flexor response) the chronaxia of the flexors is double or triple that of the extensors. If the chronaxia value of the extensor becomes greater, then extension of the great toe results.

More than likely the explanation for this change of response is central rather than peripheral on the basis of development of physiologic levels. Thus, to an age somewhere between 6 months and 1 year, there is a pure spinal reflex; then thalamopallidal control develops, but with no corticospinal effect. However, by the age of 1 year, perhaps because of myelinization of the pyramidal tract, the highest motor level has assumed control and the adult or flexor type of response is evoked by plantar stimulation. That early in life the control of movement is essentially thalamopallidal is generally accepted. The movements themselves tend to be athetotic.

In a large number of the cases in this series three points seemed to be of importance concerning the reaction of the toes: First, and what seems to us to be most important, was the strength of the stimulus, Since our instrument allowed for precise measurement of the stimulus at 0 or 30, which gave respective stimulus strengths of 80 and 250 Gm., we could exactly duplicate the stimulus in each succeeding case. In a large percentage of cases in which the lighter stimulus gave an extensor or Babinski response, the deeper stimulus gave a pure flexor response. It would seem, then, that nocuous stimuli gave flexion while lighter or innocuous stimuli resulted in extension, which could be considered the true superficial skin reflex. We have considered the flexion reflex which resulted from the painful stimulus to be a nociceptive reflex. (In this connection, however, it is interesting to note that in a number of cases a single stimulus with the point of a pin gave extension while a stimulus of sufficient intensity to cause pain but with a blunt object resulted in flexion, again a nociceptive reflex.) In those cases in which the response to the lighter stimulus was flexion, increase of the strength of the stimulus served to increase the flexor response.

A reaction which was practically constant for all babies of all ages was the result of a light transverse stimulus at the base of the metatarsophalangeal joints. This resulted in flexion of all toes. The charts show how much the percentage of flexor responses was increased in the younger children by the use of the deeper or painful stimulus. It may be well to note that although the 30 stimulus must have been

always the same, with some babies it did not seem painful while with others it seemed definitely so. It is not true, however, that only in those cases in which there seemed to be pain was there flexion when there had been an extensor reaction with the lighter stimulus. In other words, the predominant reaction to the 30 stimulus was flexion whether the stimulus appeared painful or not. Kino called attention to the fact that the stimulus must not be too strong, and also that skin reflexes fatigue easily in contrast to deep reflexes.

The second point concerns the conscious state of the individual; that is, whether the baby was asleep or awake. In the accompanying charts it will be seen that the percentage of flexor responses with both the 0 and the 30 stimulus is much higher if the infant is asleep than if it is awake. In a number of cases, the following interesting sequence of events was noted. With the child sleeping soundly and with the 0 stimulus, the reaction was flexion. With the baby partially awake, i. e., moving its extremities as though restless but with the eyes closed, and the same stimulus, the response was extension of the great toe with flexion of the others, but with the infant fully awake and crying, the same stimulus gave a pure extensor response. We have no adequate explanation for this interesting observation. However, we have noted in these instances that the muscular tone of the extremities or at least the resistance to passive movement increases as the individual comes nearer to the conscious level. This brings us again to the concept of physiologic levels—a pure spinal reflex-flexion, thalamopallidal reflex-extension, with pyramidal control-flexion. Unfortunately, we were unable to study our 6 months groups asleep. Wolpert with Vogt did not believe that this dorsal flexion was related to the Babinski phenomenon but rather that it was a pseudo-Babinski sign, in other words, an athetoid movement of the great toe.

The third factor concerns the temperature of the extremities. Frequently it was noted that the baby's foot was cold. In these instances, the reaction was markedly diminished and in some cases absent altogether. After the foot was warmed, a normal response would be obtained.

CONCLUSIONS

(*A*) 1. The intensity of the stimulus in a determination of the plantar reaction is important since it is a skin reflex. If the stimulus is too strong, there is apt to be a reversal of the reaction to flexion because of the presence of a nociceptive reflex.

2. In a large number of cases there may be a reversal of the type of reaction to the same stimulus when the subject passes from the sleeping to the waking state.

3. The condition of the subject is important: The foot should be warm and the muscles relaxed as much as possible.

(*B*) 1. The plantar reactions are variable during the first few days, but with the proper stimulus are predominantly pure extension. Extension of the great toe with flexion of the others is much more frequent than pure flexion.

2. Extension of the great toe with flexion of the others is predominant at 6 months while at this period pure flexion and pure extension about equal each other.

3. At 1 year, the reaction has become almost entirely that of the adult flexion.

4. Studies of children at various ages indicate that the change from one type of reaction to another is gradual.

FUNCTIONAL CIRCULATORY DISTURBANCES AND ORGANIC OBSTRUCTION OF THE CEREBRAL BLOOD VESSELS

WITH A CONTRIBUTION TO THE PATHOLOGY OF PERTUSSIS ECLAMPSIA *

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AND
ROY R. GRINKER, M.D.
CHICAGO

There is a noteworthy tendency in present day medicine to explain certain organic lesions on the basis of functional circulatory disturbances. In neuropathology, especially, the pathogenesis of many lesions that could not be ascribed to organic causes is now regarded as the result of functional disorders of the blood supply to the central nervous system. Whereas the German literature contains an increasing number of such observations, it is a fact that American neuropathologists have not yet directed sufficient attention to these problems.

As a result of his experiments on the effect of the various stages of nervous excitation of the blood vessels on the surrounding tissue, G. Richer [1] established a new conception of circulatory disturbances. He showed that slight stimulation of the vasomotor nerves results in a dilatation of the blood vessels with acceleration of the blood stream. Stronger stimuli lead to vasoconstriction followed by dilatation of the capillaries, and when accompanied by a slowing of the circulation, prestasis with petechiae usually occurs. This state frequently develops into a stasis. If such a stasis develops rapidly, agglutination of the blood cells may occur. A stasis is reversible and is not accompanied by transudation of serum, whereas prestasis with retardation of the blood flow, corresponding to what happens in inflammation, is associated with transudation. These states of prestasis and stasis are similar to the effect of increased excitability of the vasodilator nerves and diminution or abolition of excitability of the vasoconstrictor nerves. With exudation of serum, diapadesis of erythrocytes may also take place, and this often characterizes prestasis in the environment of a necrosis, itself

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* From the Division of Neurology and the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Richer, G.: Die Entstehung der pathologisch-anatomischen Befunde nach Hirnerschuetterung in Abhaengigkeit vom Gefaess Nervensystems des Hirns, Virchows Arch. f. path. Anat. u. Physiol. **226**:68, 1919.

caused by complete stasis. Such a combination of the necrotic effect of stasis, as in a softening with the resulting prestasis of the surrounding tissue, leads to a red infarction. When prestasis is not followed by stasis there results an incomplete necrosis with hyperplasia of the mesodermal and glial elements in the nervous tissue.

Various investigators, convinced of the importance of these experiments and conclusions of Richer, attempted to apply his conceptions to the pathology of the central nervous system. Hiller,[2] Grinker[3] and Meyer[4] have shown that the characteristic areas of softening in the brain caused by carbon monoxide poisoning occur on the basis of prestasis and stasis. In other words, functional disturbances of the blood supply lead to lesions of the nervous tissue of a severity as great as one has been accustomed to attribute only to organic circulatory disorders, as in thrombosis and embolism.

Hiller, in discussing carbon monoxide poisoning, directed attention to a peculiar necrosis of part of the cornu ammonis, the Sommer's sector, and explained it on the same basis as the other softenings. Spielmeyer showed conclusively that such a typical necrotic lesion of the cornu ammonis always occurs on the basis of a circulatory disturbance, and, as its appearance in so-called idiopathic epilepsy demonstrates, in cases that display marked functional abnormalities of the cerebral blood supply without organic vascular lesions.

It was most important to prove that these parenchymatous lesions of the brain had been caused by circulatory disturbances without a morphologic pathology of the vessel walls, and that they were not primary degenerations of the ectodermal tissue itself. Spielmeyer[5] and his co-worker Neubürger[6] were able to show that this type of lesion, especially in the gray matter, was identical with that caused by organic vascular occlusions. There is apparently a gradual transition from a reparable disturbance of brain function on a functional circulatory basis (the explanation of certain transient nervous symptoms) to permanent defects. In this large group of circulatory disorders there exist pathologic graduations from slight ganglion cell reactions corre-

2. Hiller, F.: Ueber die krankhaften Veränderung im zentral Nervensystem nach Carbon Monoxid Vergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:594, 1924.

3. Grinker, R. R.: Ueber einen Fall von Leuchtgasvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:433, 1925.

4. Meyer, A.: Ueber die Wirkung der Carbon Monoxid Vergiftung auf das zentral Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:201, 1925.

5. Spielmeyer, W.: Vasomotorisch tropische Veränderung bei cerebraler Arteriosklerose, Monatschr. f. Psychiat. u. Neurol. **68**:605, 1928.

6. Neubürger, K.: Zur Frage des Wesens und der Pathogenese der weissen Hirnerweichung, Ztschr. f. d. ges. Neurol. u. Psychiat. **105**:220, 1926.

sponding to Spielmeyer's [7] "Erbleichungen," foci in which only the ganglion cells show the results of ischemic degeneration and fade away without reactive glial response, to incomplete and complete softenings and coagulation necrosis.

It has been especially instructive to compare the anatomic changes in the nervous tissue in cases of innumerable small emboli, as occur in fat and air embolism, with those showing the same essential pathology on a functional circulatory basis. Neubürger [8] described lesions of the cortex, on the basis of embolism, which were very similar to the incomplete cortical softenings described by Alzheimer in arteriosclerosis. There were also small necroses in the white matter in Neubürger's case, but more important, typical softenings in the cornu ammonis and microglia reactions about the cerebellar Purkinje cells identical with that described by Spielmeyer [9] in functional vascular disturbances.

Neubürger's second case showed essentially the same pathology, but was caused by multiple small air emboli arising from the open uterine veins in a case of septic abortion. There resulted a more severe damage of the cortex than that in the case of fat embolism. Ischemic and homogenous degeneration of the ganglion cells, and degenerative changes of the vessel walls and glia pointed to a more severe lesion. Weimann [10] described another case of fat embolism after fracture of the femur with similar lesions. He pointed out that there were some degenerative foci in his case without fat emboli in the adjacent vessels and fat emboli in some vessels without surrounding necrosis. He furthermore found hyaline and fibrinous thrombi in certain vessels of the damaged area suggestive of a preceding vascular spasm as described by Kuczinsky and Dosquet. Weimann therefore suggested that functional disturbances of the blood supply, such as stasis and ischemia, were at least responsible for part of the damage in his case.

It is remarkable how similar the pathology in these cases of fat and air emboli is to the changes Spielmeyer described in cerebral arteriosclerosis, with its resultant diffuse functional circulatory disturbances, in hypertension associated with apoplexy, carbon monoxide poisoning, and cerebral concussion as described by Neubürger.[11] From

7. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922.

8. Neubürger, K.: Ueber Ammonshorn Veränderung bei apoplektische Hirnblutung, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:325, 1927.

9. Spielmeyer, W.: Ueber örtliche Vulnerabilität, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:1, 1928.

10. Weimann, W.: Besondere Hirnbefunde bei cerebrale Fettembolie, Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:341, 1929.

11. Neubürger, K.: Befunde bei akuten Kreislaufstoerung in die Hirninde, Zentralbl. f. d. ges. Neurol. u. Psychiat. **47**:875, 1924.

a study of this type of case, it is apparent that there exists a type of lesion in the brain, especially in the gray matter of the cortex, caused by a circulatory disturbance, which is identical in its effect on the brain tissue regardless of its organic or functional character.

This conception has been of considerable value for the explanation of lesions of the brain in various forms of eclampsia such as occur in pregnancy and certain cases of pertussis. Von Braunmuehl [12] described a case of puerperal eclampsia in which he found diffuse and focal cortical lesions and also a characteristic necrosis in the cornu ammonis. The microscopic picture corresponded essentially to that of coagulation necrosis found in air embolism. Stasis and ischemia seemed to be equally important in this case.

In regard to pertussis eclampsia, which has a mortality of 72 per cent according to the statistics of the Munich pediatric hospital, various theories have been advanced. The importance of hemorrhages of the brain has undoubtedly been overestimated in former years. Neurath [13] laid emphasis on an inflammatory nonpurulent meningitis and a cerebral edema suggestive of a nonspecific toxic disturbance similar to the reaction of the central nervous system to typhoid, scarlet fever and diphtheria.

Husler and Spatz [14] made a thorough study of two cases of pertussis eclampsia, one of which was of three days', the other of three weeks' duration. They found no meningitis but severe noninflammatory lesions, especially in the gray cortex. These affected the upper layers more than the lower ones and consisted of a homogeneous necrosis of the ganglion cells with karyorhexis and karyolysis, accompanied by progressive glial reactions and a fixed type of "Abbau." The cornu ammonis showed a necrosis in the second case, and there was some damage of the basal ganglia, the Purkinje cells and the dentate nucleus. The blood vessels were markedly dilated and revealed moderately severe proliferative changes.

Because the lesions were not focal and showed no clear dependence on the blood vessels, Husler and Spatz felt that pertussis eclampsia was anatomically a toxic encephalomalacia. We do not feel that this is a justifiable conclusion. The proliferative glial reaction need not be primary, as they stated, but reactive to the necrosis, and the lack of degenerative glial changes does not speak against a vascular etiology,

12. Von Braunmuehl, A.: Ueber Gehirnveränderung bei puerperaler Eklampsie und ihre Entstehung durch Kreislaufstörungen, Ztschr. f. d. ges Neurol. u. Psychiat. **117**, 1928.

13. Neurath, R.: Die nervoesen Komplikation und Nachkrankungen des Keuchhustens, Orbersteiner's Arb. **11**:258, 1904.

14. Husler, O., and Spatz, H.: Die Keuchhusteneklampsie, Ztschr. f. Kinderh. **38**:22, 1924.

as in nutritive disturbances of the brain various types of glial reactions are found in various regions of the lesion. The lack of circumscribed foci is not an argument against a primary vascular condition, since diffuse lesions of the cortical layers are found in cases of undoubted vascular disturbance. Moreover, the lesions of the cornu ammonis and of the Purkinje cells and the conspicuous vasodilatation seems to us in favor of the assumption that the changes in pertussis eclampsia are conditioned by circulatory disturbances and, considering the absence of organic change in the blood vessels, of a functional order.

Neubürger [15] described two other cases of pertussis eclampsia with death after three days in both cases. He found lesions similar to those described by Husler and Spatz, but in addition ischemic necrosis as in his cases of air emboli. He therefore suggested that the increased intrapulmonary pressure in violent coughing leads to a penetration of air into ruptured pulmonary vessels and to cerebral air embolism. This theory is still unproved, but the important point made clear by Neubürger is the dependence of the parenchymatous lesions on circulatory disturbances and not on a toxic reaction. Whether this circulatory disturbance in pertussis eclampsia is organic, i. e., due to air emboli, or functional can be decided only by studying a case in which the convulsions have been separated a sufficient time from the period of spasmodic coughing to preclude the possibility of air emboli.

We have been fortunate to obtain such a case and feel that its description and discussion will help in answering the pathogenesis of pertussis eclampsia. We bring in parallel to this case another one, which demonstrates the effect on the brain tissue of an embolic occlusion of a main branch of the middle cerebral artery. We chose this case for comparison because it shows clearly how an organic vascular obstruction can affect the cortex similarly to the elective lesions of the cortical layers in functional vascular disturbances.

REPORT OF CASES

CASE 1.—*History.*—D. W., a girl, aged 3 years, was admitted to the Sarah Morris Hospital on Jan. 28, 1928, because of convulsions. Seven weeks prior to admission, the patient had been in the midst of convalescence from whooping cough, completely free from coughing attacks, but had slept with difficulty and had exhibited irritability and anorexia. At that time, a first generalized convulsion with clonic movements occurred which lasted about three hours, during which time the body temperature rose to 106 F. rectally but quickly fell to 101 F. No further convulsions occurred until after an enema had been given twenty hours later. A physician then discovered that the child's left side was paralyzed. The patient, however, continued to improve. She remained free from convulsions for six weeks, although there was a continuous fever of 102 F. On Jan. 24,

15. Neubürger, K.: Ueber die Pathogenese der Keuchhusteneklampsie, Klin. Wchnschr. **4**:113, 1925.

1928, another generalized convulsion occurred, and a few hours later still another, both of only a few minutes' duration. For two days there were no convulsions; then she had one convulsion, and on the day of admission seven generalized fits were seen. A convulsion seen in the hospital by an intern was described as being limited to clonic movements of the left side of the face and of the left arm and leg.

Examination and Course.—The child was very restless and irritable, not mentally subnormal, and able to talk. Spontaneous movements were not made. The cranial nerves and ocular fundi were normal, and there was no cervical rigidity. The left anterior thigh muscles were in a state of constant twitching. When noxious stimuli were applied to the leg, it was rapidly flexed. No power was displayed in the left arm, though there was no atrophy. The abdominal reflexes and tonic neck reflexes were not obtained. The Babinski reflex was normal, and the deep reflexes were slightly more lively on the left side.

On January 15, paresis was observed on the right side. Convulsions were absent after the first few days, but the patient gradually weakened, and with unaltered neurologic symptoms, bronchopneumonia developed. She died on Feb. 25, 1928.

Laboratory Observations.—The red blood count was normal; the white count showed only 8,000 cells per cubic millimeter. The spinal fluid pressure was normal, with 27 to 31 lymphocytes per cubic millimeter, and there were normal Lange and negative Wassermann reactions. The spinal fluid sugar was 99 mg. per hundred cubic centimeters.

Necropsy.—This revealed, in general, a diffuse bronchopneumonia and a cloudy swelling of all the parenchymatous organs.

BRAIN

Examination of the Brain.—On macroscopic examination, cortical softenings were revealed on the right side beginning at the level of the rostrum of the corpus callosum and involving small unconnected areas of the frontoparietal lobes. These softened cortical areas were very friable, but the cortex maintained its shape and size and could be lifted up from the underlying softened white matter like a sequestrum. All the cortical vessels were markedly distended with blood. No evident obstruction of the larger vascular trunks could be found. On microscopic examination, the leptomeninges covering the normal cortex contained only a few large macrophages but no meningitis was present. Over the abnormal cortex, however, there were large numbers of proliferated macrophages with pyknotic nuclei undergoing regressive changes. Some of these cells contained small amounts of fat and were more numerous about the vessels. The meningeal blood vessels were distended with blood; the veins, particularly, were engorged.

The normal architectonic structure of the cortex was disturbed in many areas by a severe pathologic process which could be arbitrarily divided into three degrees of severity. Common to all was a degree of vascular dilatation so high (figs. 1 and 3) that the blood vessels were enormously ballooned out by the contained blood. The venous radicals seemed more distended. No extravasation or diapadesis could be seen, and no thrombus or embolus other than the usual agonal type was found in any vessel. Stasis was found only where the surrounding tissue was pathologically altered. Where normal brain was found, the blood vessels were of normal caliber.

The brain was not involved everywhere by the process. The greater damage was in the right hemisphere, and even here it was not uniform. Portions of the

left hemisphere were spared even a mild damage; in fact, part of the left cornu ammonis was normal. In the cortex, where the most severe grade was reached, the most severe lesion appeared in laminae III and IV. The damage was selective only in so far as in the areas of complete softening the lower laminae had usually undergone the most change, but where softening was incomplete the upper layers were usually more affected. However, in one portion the laminae III and IV were completely softened in a stripelike area, the other layers being much

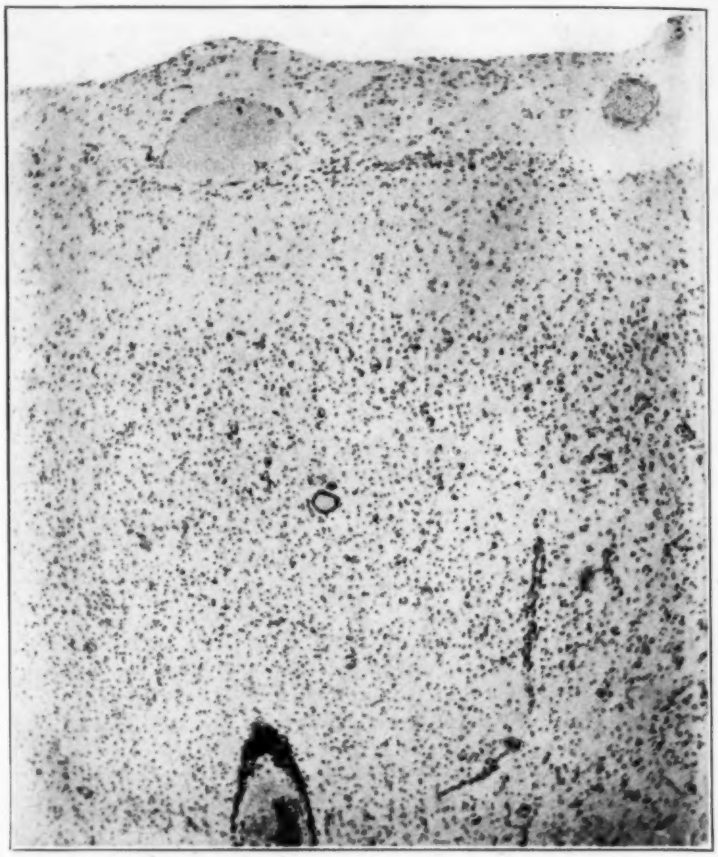

Fig. 1 (case 1).—The border of a focus showing the architectonic damage and the vascular dilatation. The ganglion cells are swollen and the macroglia are increased. Note the perivascular lymphocytic infiltration. Toluidine blue stain; × 60.

less involved. The cortical areas that were damaged were slightly more severely affected at the bottom of the sulci than at the top.

The first or mildest stage of the pathologic process was associated with a marked ganglion cell degeneration, but with only slightly disturbed architectonic structure (fig. 1). This was of a type characterized by great swelling of the ganglion cells and pyknosis of the nuclei, complete chromatolysis of the Nissl

substance, gradual dissolution of the cell outlines and fading of the cytoplasm. This was the most generalized involvement of the more mildly affected cortical areas. In the same areas a proliferation of the astrocytes in considerable numbers had taken place (fig. 2). These proliferated astrocytes revealed very insignificant regressive changes. The microglia cells were markedly increased

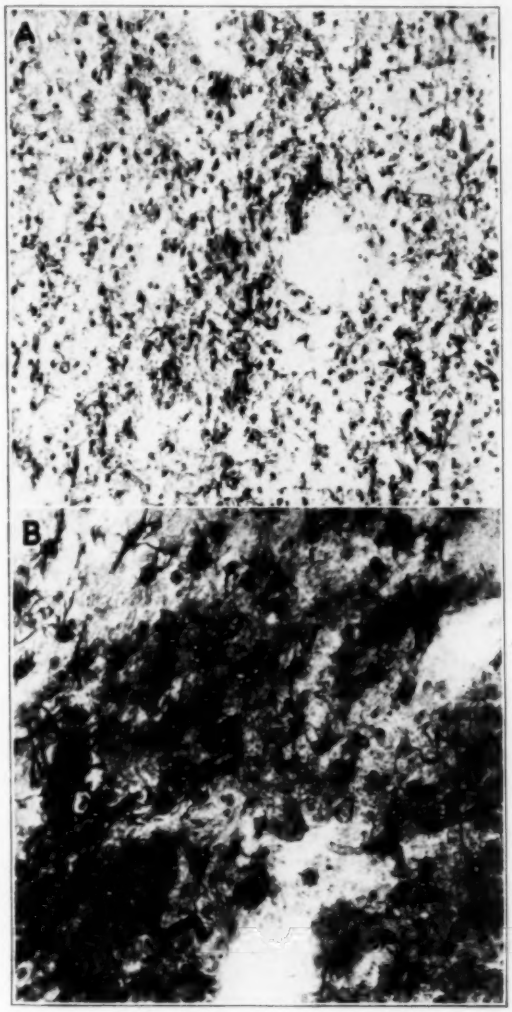

Fig. 2 (case 1).—The astrocytic proliferation in case 1: in *A*, the cortex, and in *B*, the cornu ammonis. Cajal gold sublimate impregnation.

and filled with fat, but many still maintained their oval form. This stage may be termed one of astrocytic proliferation.

A further advance in the process consisted of a still more severe ganglion cell destruction and profound alteration of the cortical architectonic structures, with preservation of but few ganglion cells (fig. 3). Neuronophagia was

well advanced, and most of the cells had disintegrated and undergone fatty changes. The astrocytes, which had proliferated enormously and formed so-called monster and giant cells, showed regressive changes. They had undergone considerable clasmatodendrosis, were swollen, rounded out and stained very faintly (fig. 4). A still more massive proliferation of the microglia had now appeared (fig. 5), and these cells showed progressive changes and the formation of typical gitter cells. The nuclei were rounded out; the processes were thicker and shorter,

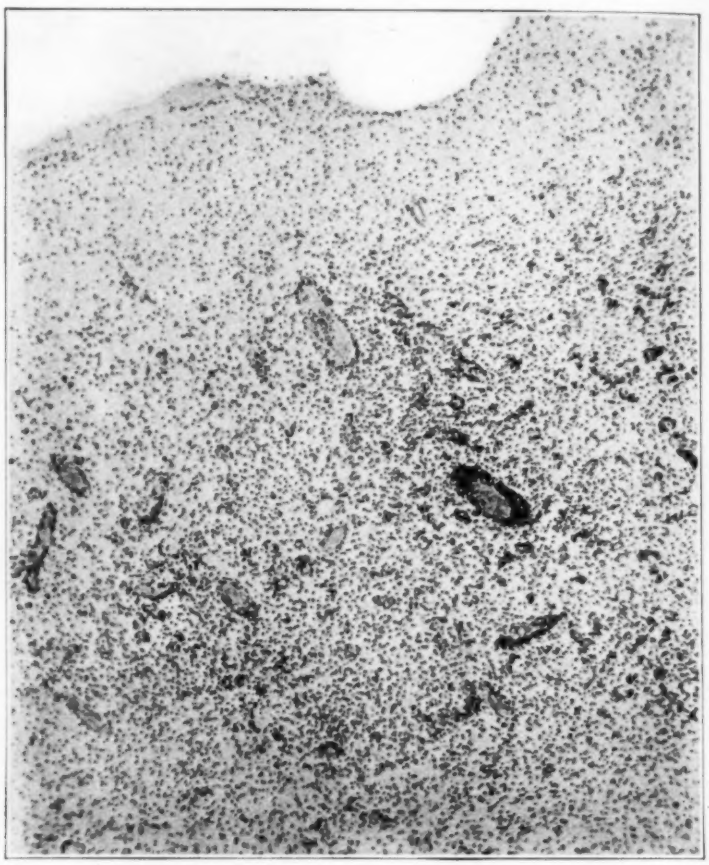

Fig. 3. (case 1).—A cortical area with incomplete softening affecting the lower layers most severely. The lymphocytic and plasma cell infiltrate can be seen. Toluidine blue stain; × 60.

and filled with fat droplets. There was much free fat present in the tissue in the form of large globules. This state may be termed incomplete softening.

The third and most severe stage of destruction consisted of complete softening (fig. 6) in which the entire tissue was free from ganglion cells and macroglia, and consisted only of free rounded fat-filled gitter cells.

In certain cortical areas the process took on another form. Here there was less astrocytic proliferation but marked diffuse increase in microglia cells, which

although not tending to round out, contained large quantities of neutral fat. This even outlined their processes, and, strangely, they demonstrated that the microglia cells seemed arranged in parallel rows perpendicular to the cortical surfaces. Lamina I frequently showed a marked proliferation of microglia when the underlying layers were uninvolved. Where the softening was more complete, the gitter cells became filled with fat and many tremendously large accumulations of fat were found free in the tissue. Fine fat lines were seen

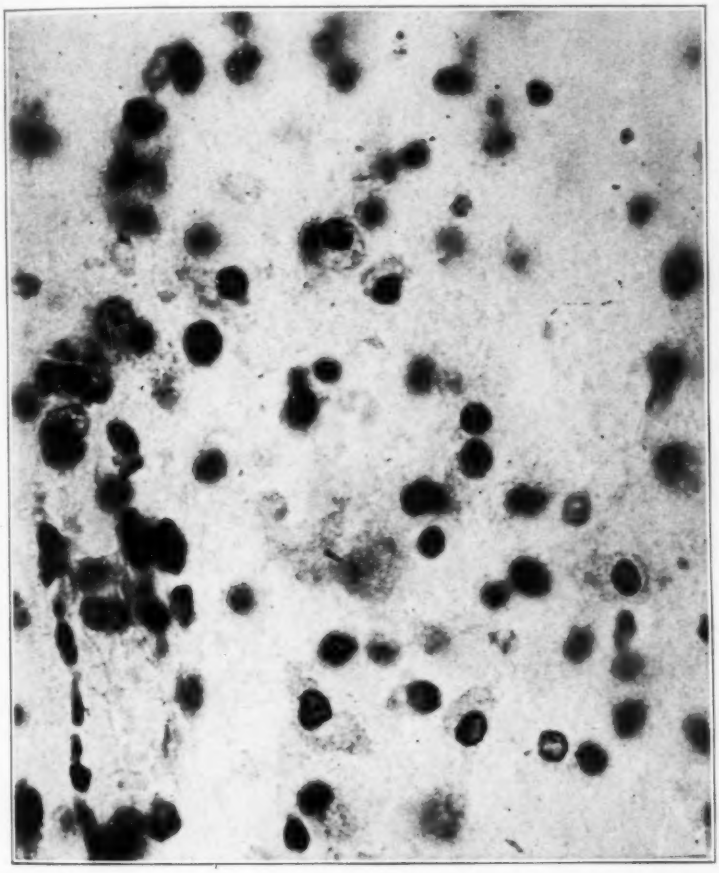

Fig. 4. (case 1).—The large number of proliferated macroglia cells with beginning regressive changes. Toluidine blue stain; × 900.

along the course of the myelin sheaths. The blood vessels were surrounded by much fat, especially in the lower cortical layers. The fat tended to be transported to the vicinity of the blood vessels of the underlying normal white matter, where it existed in the form of large coarse droplets. There was, however, no damage of the surrounding tissue.

The vascular system, aside from the marked stasis, revealed a profound proliferation and swelling of the endothelial lining. No marked new vessel formation nor any conspicuous endarteritic obliteration was noted. The most profound

endothelial damage was found in the severest softenings. Much less reaction was found with the more general and less severe cortical damage. Perivascular infiltrations of lymphocytes and plasma cells were abundant about many blood vessels, particularly in the incompletely softened areas (figs. 1 and 2). These infiltrations were not always limited to the vessels, but in adjacent areas were free in the tissue. They seemed to correspond to the state of microglia proliferation.

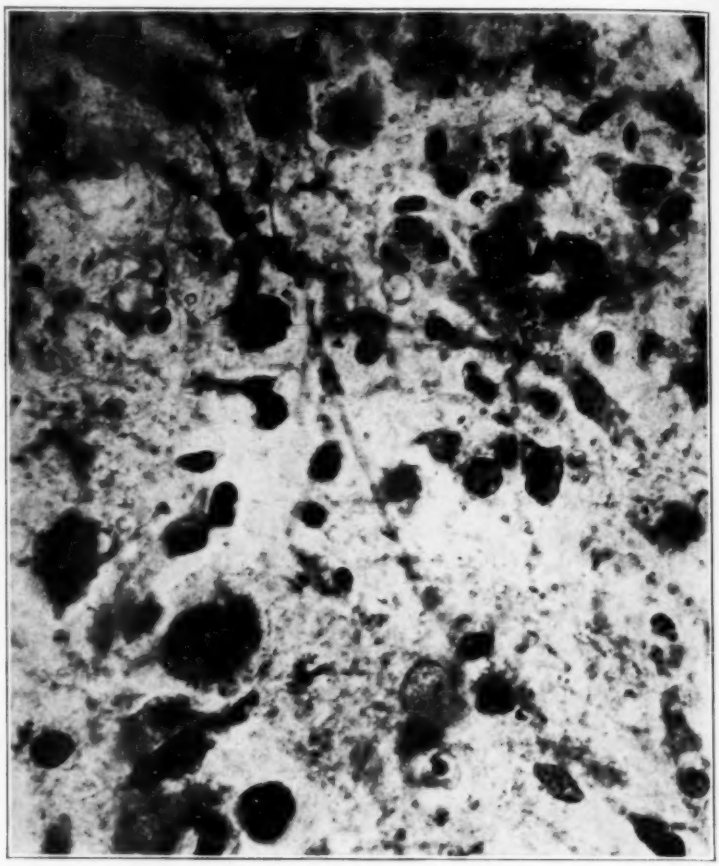

Fig. 5. (case 1).—The stage of astrocytic degeneration and beginning gitter cell formation in case 1. Toluidine blue stain; × 750.

The cornu ammonis on the left side was partially involved (fig. 7), while that on the right (fig. 8) was severely affected with total destruction of Sommer's sector, complete degeneration and falling out of ganglion cells. Two phases of reaction existed here: one in which the astrocytes were still present in proliferative stages, the other in which all ectodermal tissues had been replaced by fat-containing gitter cells, thus corresponding to the cortical lesions.

In the thalamus, the oral part of the striatum and the gray matter around the third ventricle, there were similar areas of ganglion cell degeneration with

neuronophagia and other areas of complete softening. The vessels were altered here also, in that proliferation and swelling of the endothelial linings had taken place. These structures were involved only in the gray matter and in areas close to the ventricle wall. The white matter was not implicated in the softenings.

Throughout the brain, the white matter suffered only a mild reaction in that the oligodendroglia cells were increased in number and had undergone acute

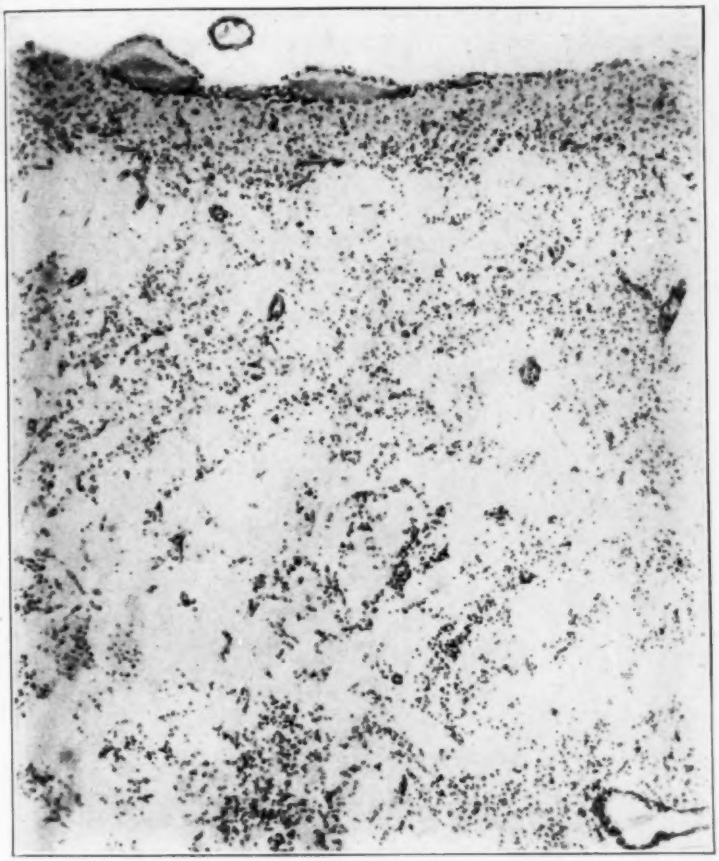

Fig. 6. (case 1).—A zone of complete softening with less involvement of the first cortical layer. Toluidine blue stain; × 60.

swelling. In this stage they showed the characteristic mucinoid degeneration [16] as described previously, and mucocytes were present, free in the tissue. The myelin sheaths and axons were unaffected, and the vascular elements revealed no abnormalities. Softenings did not occur in the white matter.

16. Grinker, R. R., and Stevens, E.: Mucoid Degeneration of the Oligodendroglia and the Formation of Free Mucin in the Brain, Arch. Path. **8**:171 (Aug.) 1929.

Comment.—In this case of pertussis eclampsia, no evidence of meningitis or hemorrhage was found. Although it is impossible to generalize from one case, we believe that clinically and anatomically these two possible causes of convulsions in pertussis probably seldom, if ever, occur. The presence of perivascular lymphocytes and plasma cells does not signify the presence of an infectious agent, as frequently such infiltrations are found near softenings in response to the chemo-

Fig. 7. (case 1).—The sharply demarcated complete softening in the cornu ammonis in case 1. Hortega's fourth variant; × 75.

taxis of the damaged tissue, and they signify inflammation in that sense only. No necessity is found to resort to the theory of pathoclisis (C. and O. Vogt) to explain the distribution of the lesion. A specific physicochemical composition of certain groups of cells, as explaining their predilection to disease, is, at best, only a working hypothesis. Here, where no isolated structure, such as one cortical layer, is alone

involved, but where the entire gray cortex in certain regions is affected, the pathogenesis is obviously a disturbance of its specific blood supply.

This case of pertussis eclampsia is the first one to be described in which the convulsions and the underlying cortical damage took place long enough after the cessation of coughing to preclude the possibility of an air embolism. No thrombus or other organic obstruction to the vessels could be found. Yet the essential pathology corresponded to the softenings typically found associated with vascular occlusions. The type of lesion varied from ganglion cell "Erbleichung" to incomplete

Fig. 8. (case 1.—The area of softening in the cornu ammonis in case 1. Note the direction of fat transport. Scarlet R-hematoxylin stain.

and complete softening, which points to a slowly increasing diminution of the blood supply. Complete tissue death did not take place, as even the center of the focus revealed a proliferative ectodermal reaction.

The lesions were confined to the cortical layers and involved them in foci. The cornu ammonis was similarly involved, but the white matter was entirely spared. This electivity is explainable by the fact that these areas have a functionally different blood supply from the white matter and deeper structures, and are notably more vulnerable to disturbances of their nutrition.

The striking observation was the tremendous dilatation of the cortical blood vessels within the softened areas, and their normal caliber in normal cortical areas. This is identical with what we have found in carbon monoxide poisoning and speaks strongly for stasis as the basis of the tissue damage.

Case 2.—*History.*—A woman, aged 47, entered the Michael Reese Hospital on March 19, 1928, in an irrational and disoriented state. A daughter stated that the patient had been in good health until a month before, when she experienced a dizzy spell of ten minutes' duration with subsequent generalized weakness. A physician prescribed digitalis for what he diagnosed as a heart lesion. Five days before admission, another spell occurred, following which the patient's speech became slurred and unintelligible. She became rapidly stuporous.

Examination and Course.—The woman was stuporous with transient periods of delirium. The facies was flushed. Many petechial hemorrhages were noted in the skin of the body, appearing in successive crops. The heart was moderately enlarged and had an apical systolic murmur. When the stupor was less pronounced it was thought that aphasia existed; correspondingly, there was no voluntary movement of the right arm or leg. The temperature ranged from 100 to 105 F. terminally. There were many urinary casts. The white blood count was 23,500; the hemoglobin 70 per cent, and the red cells 51,200,000. The nonprotein blood nitrogen was 60 mg. per hundred cubic centimeters. The blood pressure was 100 systolic and 50 diastolic. The stupor gradually increased and the patient died on March 23, 1928.

Necropsy.—There was an acute vegetative mitral endocarditis superimposed on a chronic mitral valvular lesion. There were fresh and old infarcts of the spleen and kidneys and cloudy swelling of the parenchymatous organs. A positive blood culture of *Streptococcus hemolyticus* was obtained. The anatomic diagnosis was ulcerative endocarditis and multiple emboli.

Examination of the Brain.—On macroscopic examination, there was found a superficial softening of the left superior and middle temporal gyri, involving only the cortex, extending from the prerolandic area back to the gyrus angularis. The inferior frontal gyrus was also softened from the same anterior limit backward on its under surface, involving the insula and extending to the inferior parietal lobule and involving it in the calcarine region. These gyri, although soft to the touch, edematous and of a darker gray color, maintained their normal shape and seemed lifted up from the white matter as sequestrums. The white matter was uninvolved. The meninges were normal and there was no hemorrhage. In the right middle temporal gyrus, anterior to the inferior horn of the lateral ventricle, was a small cavity, 1 cm. in size, lined with smooth walls and surrounded by softened tissue. The common trunk of the middle cerebral artery just before its division into the ascending parietal, parietotemporal and temporal arteries, was occluded by an antemortem thrombus.

On microscopic examination, it was found that in the space between the temporal lobe and insula, the vessels supplying the temporal and parietal lobes were thrombosed. The thrombi were stratified, composed of a layer of red cells and fibrin, a layer of white cells and then a mixture of red and white cells. Blood pigment was present within the thrombi. One of the branches had ruptured at the thrombosed site, forming a dissecting aneurysm containing coagulated blood between the media and adventitia. The arteries distal to the thrombosed

trunk contained no blood, and their walls were thickened. One branch was completely obliterated by proliferated endothelium, and the large veins were empty.

The cortical changes to be described were localized to the areas grossly seen to be soft and edematous. The essential type of lesion was apparently an edema with partial necrosis of the tissue. There was a surprisingly sharp demarcation between the areas affected and the adjacent cortex and the white matter, so much so that the gross appearance of partial sequestration of the cortex was explained (fig. 9). The meningeal arteries contained very little blood over the areas

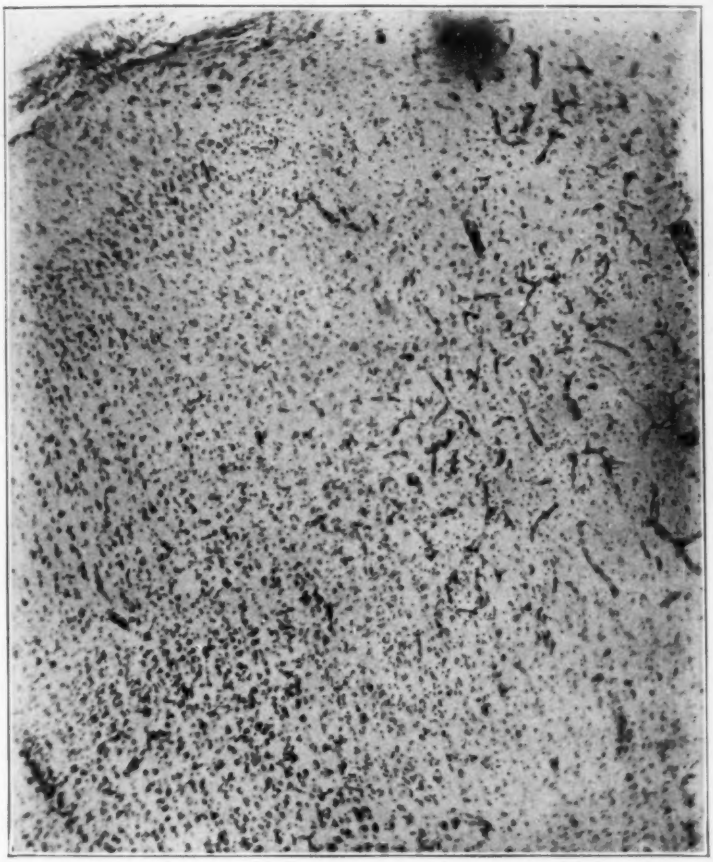

Fig. 9. (case 2).—The cortex in case 2 showing the sharp demarcation between normal and pathologic tissue. The proliferative vascular reaction of the bordering zone can be seen. Toluidine blue stain; × 60.

involved, and the meningeal connective tissue and its contained macrophages were moderately increased.

The normal cortex showed throughout a general, rather mild reaction which has been described elsewhere as a toxic reaction.[17] The architectonic structure

17. Grinker, R. R., and Stone, T. T.: Acute Toxic Encephalitis in Childhood, Arch. Neurol. & Psychiat. **20**:214, (Aug.) 1928.

was, however, well preserved. The ganglion cells were moderately swollen and the Nissl substance faded. There was a slight diffuse proliferation of the true glia with increase in the perineuronal satellites. The white matter throughout revealed no softenings or marked change, even in those locations beneath the altered cortex. The oligodendroglia cells were proliferated and had undergone mucoid degeneration to a large extent.

Proceeding toward the damaged tissue (fig. 10), the first zone was characterized by a decrease in the number of the ectodermal elements. The cell elements were widely separated and surrounded by large vacant spaces; the myelin radi-

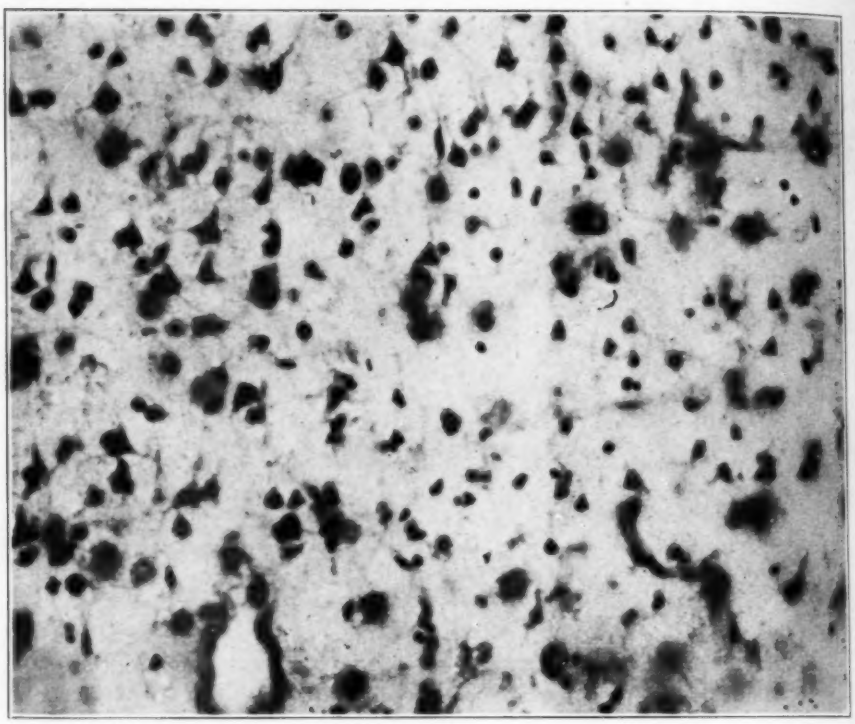

Fig. 10 (case 2).—Going from left to right the border zone is approached. Note the increasing degeneration and falling out of ganglion cells and the marked astrocytic proliferation. Toluidine blue stain; × 300.

ations were spread widely apart and decreased; all this was typical of a localized edema. The ganglion cells were markedly swollen and had undergone some absolute diminution. The macroglia cells were markedly proliferated as in the border zone of case 1 and formed large protoplasmic-rich clusters (fig. 11). No microglial reaction was noted, except in the subpial cortical layers, where only a slight proliferation with the formation of a few fat-containing gitter cells could be found. In this same region a more typical type of ischemic degeneration was found among the ganglion cells. This whole first zone formed only a very narrow margin.

The second zone showed a striking progressive change in the blood vessels (fig. 12). They revealed a notable increase and swelling of the endothelial lining cells. There, lumens were practically obliterated, although some vessels contained a few visible erythrocytes. The vessel walls took on a prominent blue color with basic dyes. There was no residue of the normal architectonic structure. The ganglion cells were swollen, and homogeneous degeneration had taken place; their Nissl substance showed marked chromatolysis. The cells were remarkably rich in lipoid pigment. The astrocytes were proliferated to giant cells, and multinucleated cells were seen. The microglia cells, on the other hand, were much

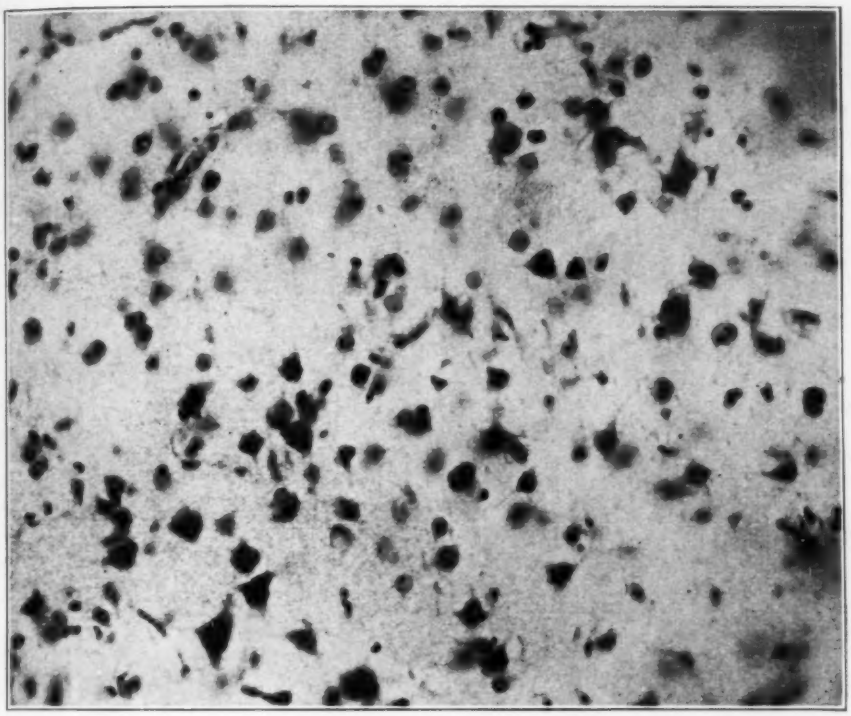

Fig. 11 (case 2).—The stage of astrocytic proliferation with very few microglia cells. The ganglion cells are markedly decreased. Toluidine blue stain; ×300.

fewer and showed no tendency to development of gitter cells, but contained shrunken pyknotic nuclei and faintly staining processes, evidences of regressive changes.

The central zone of the lesion showed only regressive changes (fig. 13). It is apparent that the deeper layers of the cortex were more profoundly affected. The ganglion cells had mostly disappeared with, of course, no remnant of architectonic structure, but the cortex had maintained its form and showed no softening. It was, however, greatly increased in depth, due to edema. The few remaining ganglion cells showed a typical ischemic degeneration. Their cell bodies were thin and shrunken to an angular shape. The cytoplasm was heavily

stained, and the nuclei were small and pyknotic. There was a marked increase in fatty pigment within the remaining ganglion cells.

Microglia cells were very few and apparently rapidly disappearing, with regressive changes. No formation of gitter cells could be observed. The astrocytes, too, were undergoing profound regressive changes, relatively few remaining. They had undergone complete clasmatodendrosis; their cytoplasm had shrunken and rounded out, and the nuclei were faded.

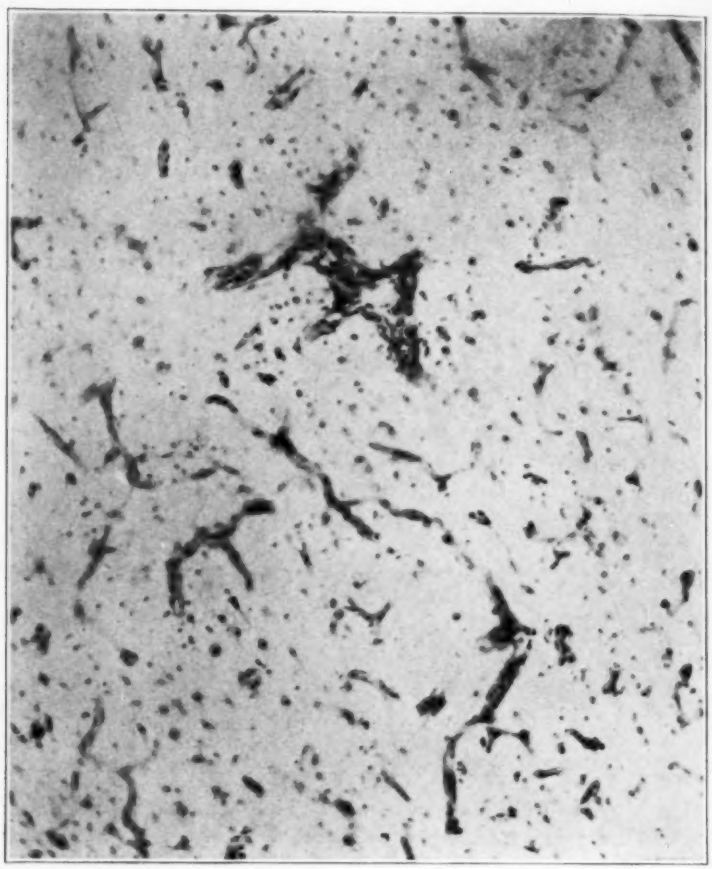

Fig. 12.—The zone of mesodermal proliferation with a deeply stained, hyperplastic, empty blood vessel. The degenerating astrocytes can be made out as well. Toluidine blue stain; × 140.

The precapillaries and larger blood vessels revealed a gradation of changes, transient from the progressive to regressive states. They stained very poorly and were markedly decreased in number, seemingly having faded out. The endothelial cells were swollen and very indistinct in outline; many had lost their nuclei. Approaching the marginal zone from the most severely affected areas, a change in the vessels was evident. They were almost bloodless, but toward the periph-

ery of the lesion, from the zone of almost complete absence of microglia and degeneration of astrocytes toward the zone of regressively altered microglia and proliferated astrocytes, the endothelial lining of the vessels was more sharply outlined. The marginal vessels showed more proliferative changes, while those in the center of the focus were degenerated. The endothelial cells became more numerous and swollen. The capillaries themselves in the central zone had to a considerable extent degenerated and disappeared.

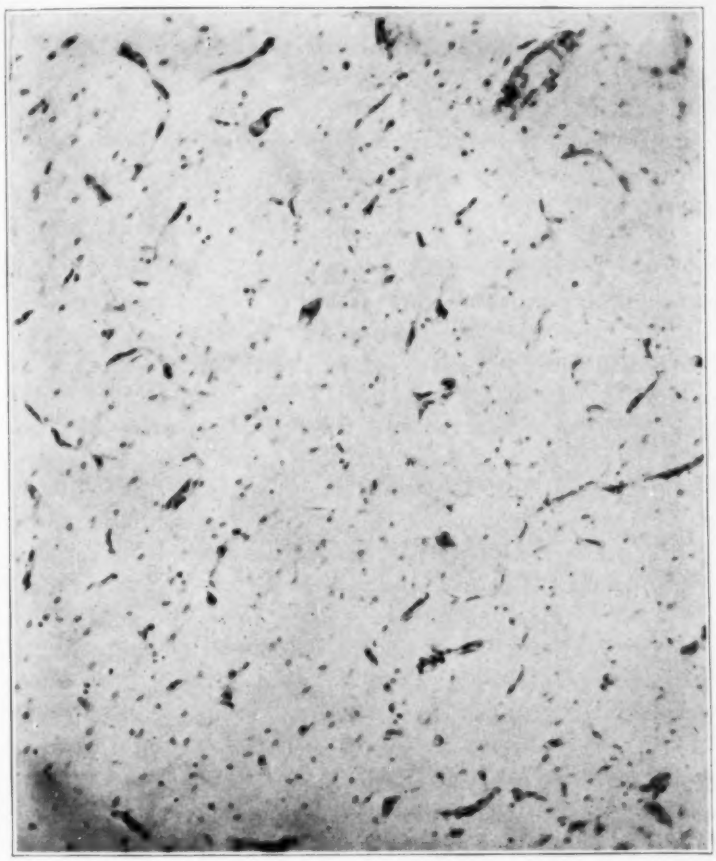

Fig. 13. (case 2).—The center of the focus showing the almost complete death of the nervous parenchyma with the preservation of but few degenerating blood vessels and fat filled ganglion cells. Toluidine blue stain; × 140.

Comment.—It has been definitely shown that this interesting case had at its basis an apparently total occlusion of a large branch of the middle cerebral artery. Probably, a sudden rather large embolus was first lodged, with subsequent thrombosis. The distal vessels were to a great extent bloodless and obliterated. The result was a fairly sharply demarcated edema with central necrosis of the cortical gray substance

in the regions supplied by branches of the occluded vessels. Here again, the white matter, functionally supplied from another vascular source, remained free from damage.

The pathologic details of the lesion are worthy of some discussion. Its general appearance was that of a partial edema of the gray cortex on the basis of a severe ischemia of the areas involved. By imbibition of fluid into the tissue, the ischemia had led to a severe damage of the ectodermal elements, but with a slight proliferative reaction. A profound increase took place, however, in the lipoid pigment content of the ganglion cells. It is especially interesting that under such pathologic conditions the microglia failed to respond by proliferation. The proliferative changes of the vessel wall elements can be explained only on the basis of the ischemia in association with the circulating toxic products, part of the general sepsis.

This type of reaction of the gray cortex demonstrated that total necrosis can be brought about not only by softening or coagulation, but also by a severe edema due to ischemia. It is astonishing that such a pathologic change can take place in a rather isolated area of the brain and can be confined to the gray matter only. The pathologic details of the ectodermal elements, except for the increase of lipoid within the ganglion cells, is very similar to what occurs in postmortem autolysis of tissue, in which the cell elements disappear slowly. An analogous condition existed in this case with the almost total sequestration of the tissue from its blood supply. This alone can explain the absence of microglial proliferation, which in necrosis apparently depends on the intravital neutral fat formation from the higher lipoid compounds of the myelin sheaths for its stimulus.

The bordering areas of the lesion showed the usual cortical reaction to disturbances in nutrition. The astrocytic proliferation was similar to that found in case 1. In the second zone, the mesodermal progressive reaction was made possible, probably by a persistent slight blood supply, yet not sufficient for an ectodermal reaction, for here the astrocytes were all rapidly degenerating. The absence of a microglia reaction in the presence of this mesodermal vascular reaction is surprising in view of the present conception of a mesodermal source of the microglia.

SUMMARY

A comparison of these two almost similar cases shows how distinct areas of gray cortex can be destroyed by both organic and functional disturbances of the blood vessels. In one case, a demonstrable organic ischemia of a large pial vessel took place, with rapid and severe edema and necrosis of the supplied tissue. In the other case, a more gradual and less complete disturbance of the nutrition due to stasis resulted. Therefore the type of response of the ectodermal reactions differed.

When the nutrition is severely damaged, due to ischemia and edema, death is so complete as to preclude ectodermal reaction. However, the general process in both cases led to a damage of the gray cortex.

The result of disturbance of a large pial vessel, whether on a functional or an organic basis, leads to a severe damage of the gray cortex and not of the white matter, with a predilection for the deeper cortical laminae. The sharp border between normal white matter and involved cortex speaks against the purely anatomic proof of Pfeifer,[18] who denies the presence of end-arteries in the brain and postulates a diffuse arterial network. From a functional standpoint, pial arteries supply almost exclusively gray matter and within the gray matter, only certain definitely demarcated areas are supplied by an individual large pial artery.

Stasis as the basis of the lesions in the pertussis case could be objectively demonstrated. The reason for the development of such stasis is not obvious except if it be, as in carbon monoxide, due to the action of a circulating noxious agent on the vessel walls. The question of the necessity of a vasomotor nerve supply to the intracerebral blood vessels in order that functional vascular disturbances may occur is not for us to argue. The anatomic work of Stöhr, Jr.,[19] and Hassin [20] and the experimental work of Forbes and Wolff [21] have shown that in all probability the pial vessels are under vasomotor control, and modifications of their caliber result in a secondary alteration of the cerebral capillary bed. Should this be incorrect, the cerebral vascular bed is probably capable of reacting by direct chemical or mechanical stimuli as Florey [22] has shown.

To the conception of a functional moment in the production of many vascular disturbances of the brain more attention should be directed. The etiology of many obscure transient nervous syndromes and of severe anatomic lesions of the brain without apparent organic cause may be solved by further study of the possibility of functional circulatory disturbances.

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A SERIES OF PITUITARY PICTURES

COMMENTARIES ON THE PATHOLOGIC, CLINICAL AND THERAPEUTIC ASPECTS *

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Though Horsley, in one of his surgical treatises, incidentally referred to four cases in which he approached the pituitary lesion by the temporal route, many years have elapsed from that time to the present, when the management of pituitary lesions has become an acknowledged activity in the neurosurgical clinic. The first operation on the pituitary gland in my clinic was performed in 1912, and since then I have entered 231 cases on my pituitary register. Of these, 129 are primary pituitary lesions, 21 pharyngeal duct lesions, 37 suprasellar lesions and 44 are cases of pituitary dysfunction. In the latter group are included cases with obvious pituitary dysfunction, but without any evidence of a gross lesion of the pituitary itself or of the pharyngeal duct. The management of these cases will become of greater interest when reliable extracts become available.

Rather than confine my remarks to a distinctive field, physiologic or pathologic, I have elected to present a series of cases selected as illustrative of different types of pituitary syndromes, with a running commentary on their noteworthy features.

EPITOME OF SERIES

Case 1: Adenoma with relief by irradiation. Under observation three years.

Case 2: Pharyngeal pouch cyst, with pituitary cachexia, relieved by operation. Under observation three years.

Case 3: Adamantinoma, with relief from symptoms by operation. Under observation three years.

Case 4: Adenocarcinoma, widespread, invading sinuses and posterior fossa. Operative fatality after enucleation of posterior fossa.

Case 5: Adenoma with pronounced signs of hypopituitarism. Operative recovery. Striking effects of glandular feeding. Under observation four years.

Case 6: Adenocarcinoma with complete relief from symptoms and restoration of menses. Under observation eight years.

Case 7: Pituitary cyst with symptoms preceding enlistment in U. S. Army, 1918. Recovery following transsphenoidal evacuation. Under observation eight years.

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* Submitted for publication, Sept. 15, 1929.

* From the Neurosurgical Clinic of the University Hospital.

Case 8: Adenoma, transsphenoidal approach with relapse; transfrontal extirpation with recovery. Patient under observation thirteen years from second operation and twenty-six years from onset of first symptoms.

Case 9: Adenoma with marked visual disturbance but without pituitary stigmas, relieved by operation. Under observation two and one-half years.

Case 10: Adenoma of enormous size, with a polyglandular syndrome and visual hallucinations, with recovery following a right and left craniotomy.

REPORT OF CASES

CASE 1.—*A patient of middle life, whose vision had been failing for five years, with evidence of a primary pituitary lesion, as indicated by the roentgen ray and by visual fields, but without any but trivial pituitary stigmas, possibly slight fatigability and tendency to sleep longer, was given three courses of irradiation. Three years and nine months after the treatment was instituted, there are no signs of further pituitary dysfunction, but sustained improvement in fields and vision. Pathologic diagnosis: presumably an adenoma.*

History.—N. S., a woman, aged 50, was admitted to the neurosurgical service of the University Hospital on Jan. 30, 1926. She had had sick headaches since early youth, but of late these had been less frequent. During the past few years, vision had been gradually failing. With the failing vision there had been no headaches, vomiting or other complaints. In July, 1925, she was told that there were signs of optic atrophy, and since that time her vision had become more and more impaired. The patient had had measles, scarlet fever, pertussis, diphtheria, influenza and pneumonia. The menses were established at 12 years, and were regular and painful. The menopause occurred five years before examination. She was married at 31, but there were no pregnancies.

Neurologic Examination.—There was no disturbance of motor or sensory function; the tendon reflexes were normal, and there was no cranial nerve involvement, save of the second.

Pituitary Signs.—Roentgen ray: There was atrophy of the dorsum sellae and posterior clinoid processes with enlargement of the sella turcica and encroachment on the sphenoid sinus (fig. 1).

Basal Metabolic Rate: The rate was plus 4.

Ophthalmologic: There was a yellowish waxy atrophy of both disks. Vision on the right was 6/22; on the left, 6/30.

Fields: There was a relative scotoma about 15 degrees in the horizontal meridian, extending from the midline templeward to the blind spot in the right eye and a little short of it in the left; between 10 and 25 degrees in the vertical. There was slight contraction of the fields. These scotomas indicated a beginning bitemporal hemianopia.

Endocrine: There were no manifest pituitary stigmas, either of anterior or of posterior dysfunction, unless it be that she slept longer than she used to.

Roentgen Treatment.—In February, 1926, the patient was given a first course of deep therapy irradiation through each temporal region (fig. 2).

Readmissions.—(1) On April 26, 1926, the patient was readmitted to the University Hospital and was given a second course of irradiation. Since the previous admission, Jan. 30, 1926, she had gained 10 pounds (4.5 Kg.) despite a rather restricted diet. Her present weight was 184 pounds (83.5 Kg.). Vision at this time was: left eye, 6/30 and right eye, 6/15 as compared with right eye, 6/22.

There were no striking changes in the fields. The basal metabolic rate was minus 13 as compared with plus 4. (*2*) On August 3, the patient had not gained in weight since the last admission. The basal metabolic rate now was minus 20. Vision was: left eye, 6/22 (formerly 6/30), right eye, 6/15, unchanged. She received a third course of irradiation.

Comment.—One not infrequently sees subjects with pituitarism with manifest evidence of an adenoma of not inconsiderable dimensions without any striking symptoms other than failing vision, but this case has been chosen chiefly as illustrative of what may be accomplished in

Fig. 1 (case 1).—Deformation of the sella turcica, typical of the primary pituitary lesion, with almost complete obliteration of the sphenoid sinus.

the exceptional case by irradiation. There is no question in my mind that had irradiation not been employed the optic atrophy would have advanced and vision deteriorated, terminating in total blindness. Apart from the improvement in vision, other beneficial effects were noted. The patient was fatigued less easily and felt as vigorous as she did ten years before. She gained 10 pounds during the treatment, only to lose it again. During the course of the three years, the metabolic rate dropped from plus 4 to minus 20, but I shall comment on the question of basal metabolism elsewhere.

The outstanding features in this case were the improvement in vision (left eye, from 6/30 to 6/22; right eye, 6/22 to 6/12) and expansion of the fields, without signs of relapse more than three and one-half years after the treatment was instituted (figs. 3 and 4).

Under what circumstances is one warranted in trying the effects of irradiation, with the risk of what delay in operation may mean? To answer this question one must consider not so much the field distortions as the appearance of the disk. If the signs of atrophy are not too far advanced and if, with repeated examinations, the capillarity of the disks remains more or less unchanged, one can with propriety postpone operation. To be sure, it is not often that one sees patients in whom vision is so well preserved as in this case. At the first consultation, many of our patients are already blind in one eye and vision

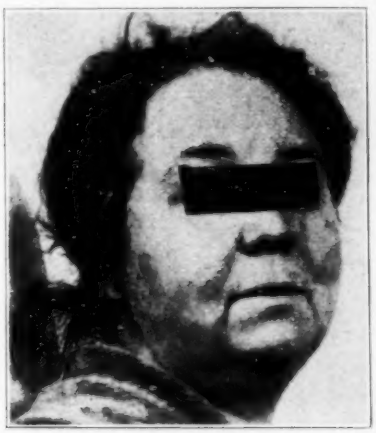


Fig. 2 (case 1).—Photograph of patient when roentgen treatment was inaugurated.

is rapidly failing in the other. That is a different story and procrastination under those circumstances is never justifiable. Irradiation, of course, will have no influence on a lesion already cystic, but obviously there is no way, except by operation, of determining the precise nature of the lesion.

This is the only case in my experience in which the beneficial effects of irradiation have been sustained. In a few other cases there was improvement at first but later relapse. Hence a word of warning to those who do not know the limitations of irradiation as a means of conserving vision in the subject with pituitarism.

CASE 2.—*A man in his twentieth year, with a history of arrest of growth when 7 and failing vision when 10 years of age, presented a picture of hypophysary cachexia. Eighteen months after an operation on a tumor of the pharyngeal pouch, the patient had grown 6 inches, from a state of apathy and lethargy had become active and alert, had acquired sex characteristics, had gained in weight and had recovered vision. Pathologic diagnosis: pharyngeal duct cyst.*

History.—A man, aged 20, was referred by Dr. A. G. Fewell to the Neurosurgical Service of the University Hospital on March 5, 1926. His father, mother and four brothers were living and well. There were no suggestions of any endocrine disorder in the family. When 7 years of age (1913), it was

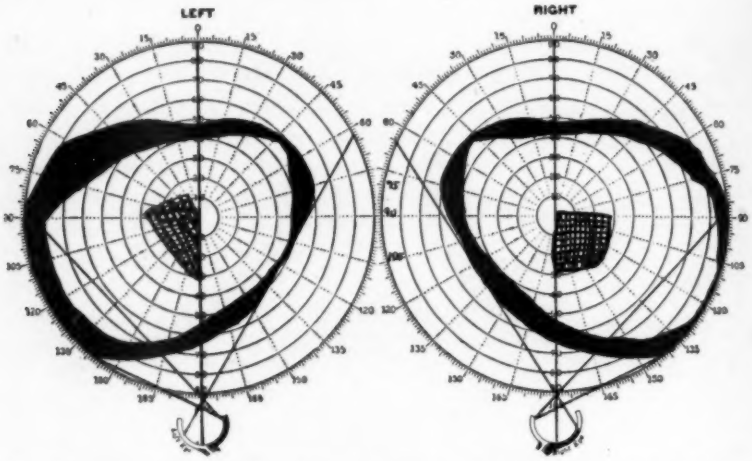


Fig. 3 (case 1).—Bilateral scotomas before roentgen treatment was inaugurated. Vision: left eye, 6/30; right eye, 6/22.

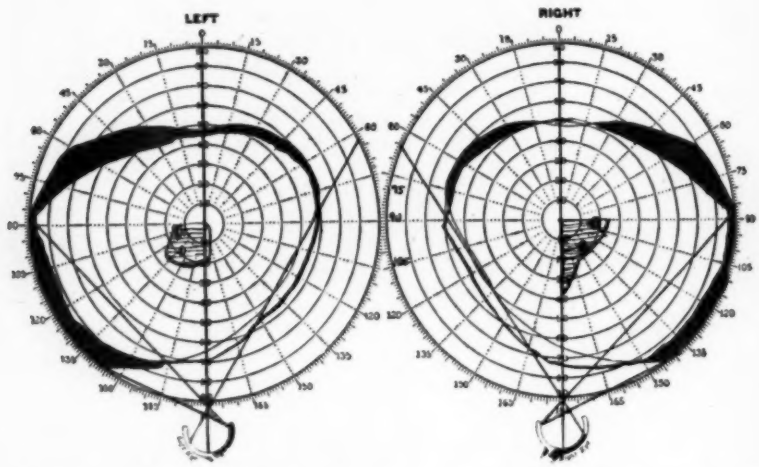


Fig 4 (case 1).—Scotomas disappearing under roentgen treatments and vision improving; right eye, 6/12; left eye, 6/22 (Dec. 15, 1927).

noted that the patient began to fail somewhat in health, complained of being weak and of having little energy. He continued rather irregularly at school for two or three years, and finally, as his health did not improve, he was taken out of school. He complained then of headaches and trouble with his eyes. From that time (1916) on, he had done little if anything, living mostly in the woods, occasionally doing

odd jobs with his father. It was noticed then that his growth was retarded. There was very little change from that time until July, 1925, when headache became much more severe and frequent, and vision began to fail rapidly. Recently, because of headache, he had been confined to bed. He vomited twice in the week prior to admission.

Physical Examination.—Though the age was 20, the patient had the appearance of a boy of 14, apparently undernourished and underdeveloped, with sallow complexion. The thorax was contracted; the heart and lungs were normal. The musculature of the extremities was poorly developed.

Neurologic Status.—There were marked mental apathy; no disturbance of sensation and no paralysis; no disturbance of coordination or gait; no pathologic reflexes.

Pituitary Signs.—Roentgen ray: The sella turcica was 7.5 by 11 mm.; there was an area of calcification in the meninges of the right parieto-occipital region.

Pituitary Stigmas: The skin was dry and scaly; there was no hair on the face or in the axillae and scanty hair over the pubis; the genitalia were underdeveloped; the basal metabolic rate was minus 12.

Ophthalmologic: The media were clear. The disks were somewhat yellow, the margins well defined. The pupils were unequal, 4 mm. on the right and 3.5 mm. on the left; the left reacted less promptly to light. Vision was: left eye, 6/30; right eye, 6/15. Bitemporal hemianopia was present.

Operation.—On May 1, 1926, a transfrontal craniotomy was performed on the right, under ether anesthesia. A cyst was exposed, evacuated and most of the capsule excised. On reflection of the flap, the vascular grooves were seen to be unusually deep; the middle meningeal vessels stood out prominently on the dura and oozed freely from many points. The anterior horn of the ventricle was tapped, a moderate amount of fluid evacuated and the frontal lobe elevated without difficulty. There appeared at once the capsule of the lesion presenting between the two optic nerves. The distance between the optic foramen and the chiasm was at least 3 cm. With an aspirating needle a thick yellowish fluid, with all the gross appearances of pus, was evacuated. On the anterior wall of the capsule there appeared to be a thin layer of what might have been adenomatous tissues. A considerable portion of the capsule was removed.

Throughout the postoperative convalescence, the patient was exceedingly drowsy, sleeping most of the time. Microscopic examination of the fluid removed from the cyst revealed pus cells and diplococci, but the cultures were negative. He was dismissed from the hospital on June 2, with a discharging sinus, having had an active wound infection *(Staphylococcus albus nonhemolyticus)*.

Readmission.—On Jan. 10, 1928, the patient returned with the sinus still discharging. During this interval of eighteen months there had been a striking change for the better. He had gained steadily in strength, and had grown 6 inches; he was mentally alert and was acquiring sex characteristics. He was physically active; headaches had disappeared, and visual acuity had improved (formerly, left eye, 6/26, and right eye, 6/15, now, left eye and right eye, 6/6). There was only a slight defect in the visual fields (figs. 5 and 6).

Comment.—Certain features in this case at once arrest attention. The life history of the lesion is interesting. Thirteen years before the operation there were signs of arrest of growth and physical weakness, and yet despite this long period of pressure the optic nerves had not

suffered irreparable damage. After removal of the tumor, vision improved from 6/30 in the left and 6/15 in the right eye to 6/6 in each eye.

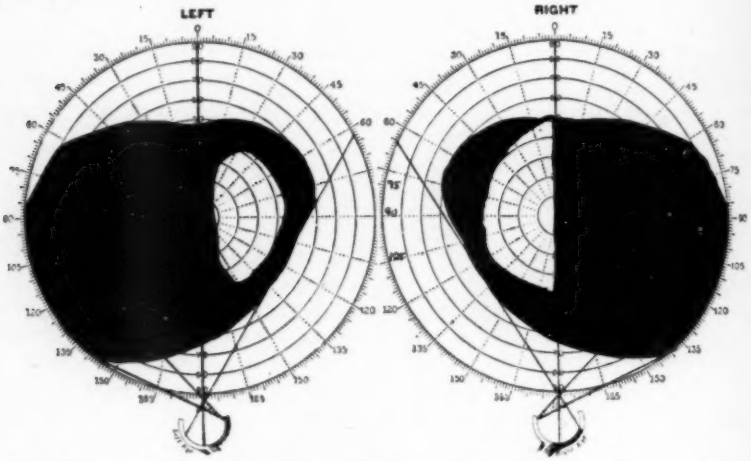


Fig. 5 (case 2).—Fields before operation, April 26, 1926. Vision: right eye, 6/15; left eye, 6/30.

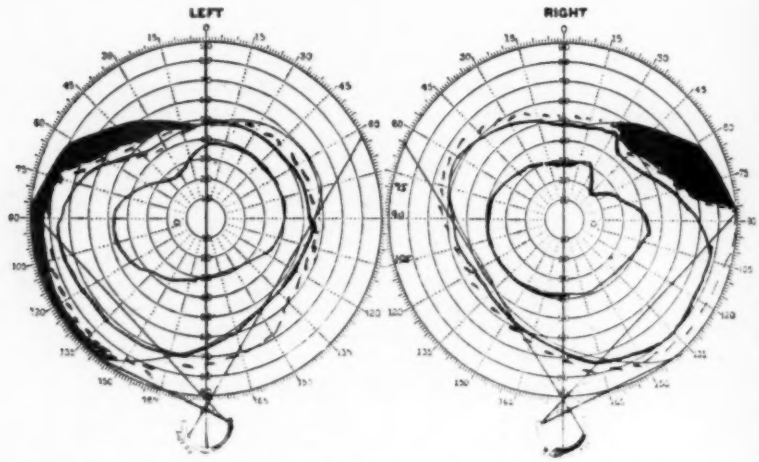


Fig. 6 (case 2).—Fields twenty months after evacuation of pituitary cyst and removal of capsule, Jan. 11, 1928. Vision: right eye, 6/6; left eye, 6/6. Compare with figure 5.

The absence of any enlargement of the sella turcica suggested a tumor of the pharyngeal duct rather than a Rathke's pouch cyst or primary pituitary lesion. Cysts arising from Rathke's pouch, as Peet[1]

1. Peet, Max Minor: Pituitary Adamantinomas: Report of Three Cases, Arch. Surg. **15**: 829 (Dec.) 1927.

said, develop between the anterior and posterior lobes and are therefore primarily intrasellar; the roentgen rays would reveal some deformation of the sella turcica. In this case the sella was not enlarged.

In my experience, the patient with a tumor of the pharyngeal duct exhibits signs of hypopituitarism rather than hyperpituitarism and symptoms of the Fröhlich syndrome, in which lethargy, accession in weight and impending blindness prevail. In this case, while there were signs of infantilism with arrest of growth, emaciation with poorly

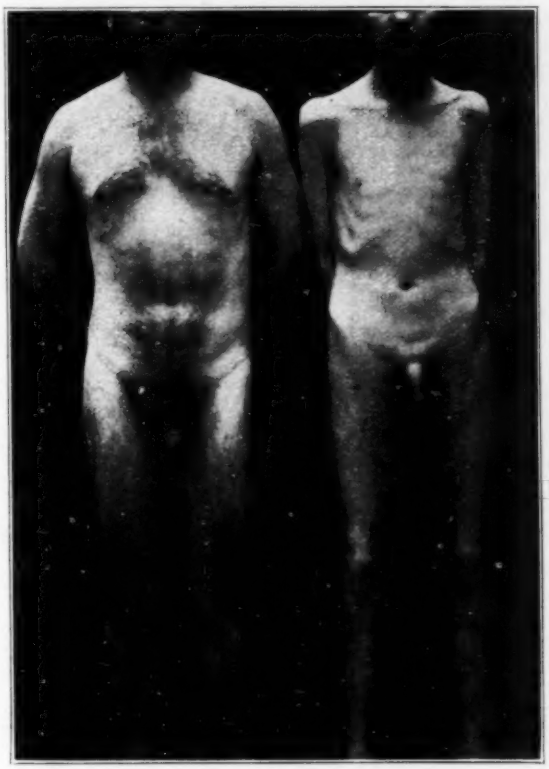


Fig. 7 (case 2).—Photograph of patient with normal man before operation.

developed musculature was a conspicuous feature. It is not without interest to note that in the course of eighteen months after removal of the tumor, the patient grew 6 inches and began to acquire sex characteristics (figs. 7 and 8).

This case has a peculiar interest in that it has many of the characteristics of the hypophyseal picture first described by Simmonds [2] as hypophysary cachexia. In my entire series there are but two striking

2. Simmonds: Deutsche med. Wchnschr. **40**:322, 1914.

instances of this pituitary syndrome. While the underlying pathology may vary—septic embolism, tuberculosis, syphilis, tumors and cysts—it has been maintained that the syndrome is due to more or less complete destruction of the anterior lobe. While the outstanding symptom of hypophysary cachexia is loss of weight, there are many other asso-

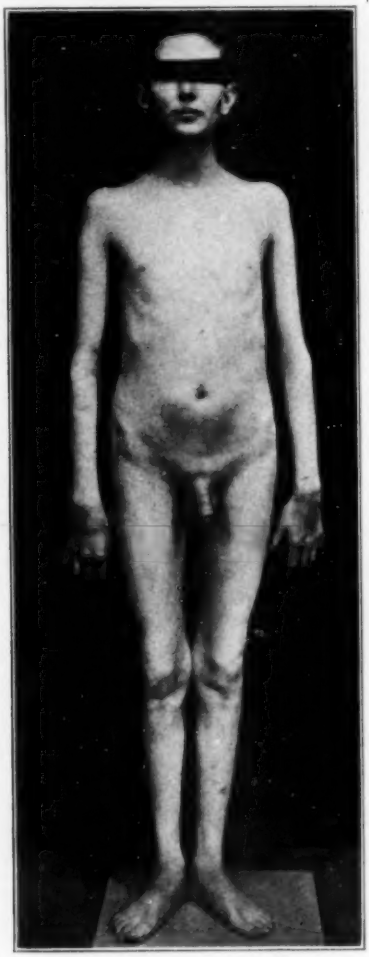


Fig. 8 (case 2).—Photograph of patient twenty months after operation.

ciated symptoms: vasomotor and trophic disturbances of the skin, loss of teeth, falling out of hair and great muscular weakness, so pronounced in case 2. The blood pressure may be low, and there may be anemia, sexual disturbances and nervous and psychic disorders. No doubt part of the picture may be, as in other pituitary syndromes, the result of a polyglandular insufficiency.

CASE 3.—*In a woman, aged 33, a course of roentgen treatments failed to prevent deterioration of vision. With three years of headache and six months of failing vision, amenorrhea was the only pituitary stigma. Following an operation, the visual acuity advanced from 2/60 in each eye to 20/20 in the right and 20/30 in the left eye. Pathologic diagnosis: adamantinoma.*

History.—A woman, aged 33, was referred to the neurosurgical service of the University Hospital by Dr. William G. Spiller, on Dec. 16, 1926. She had had the usual diseases of childhood and, in addition, erysipelas at the age of 7 and pneumonia at 12. There was no record of any endocrine disturbance in the family. The patient had been married thirteen years, had had no miscarriages and had one living child. Menstruation began in the twelfth year, and had been regular until three months before examination.

In October, 1923, the patient began to have a dull, midfrontal headache. The headaches, though not as constant as they were, were more severe and associated with pain over the right eye. On June 1, 1926, the patient became aware of a

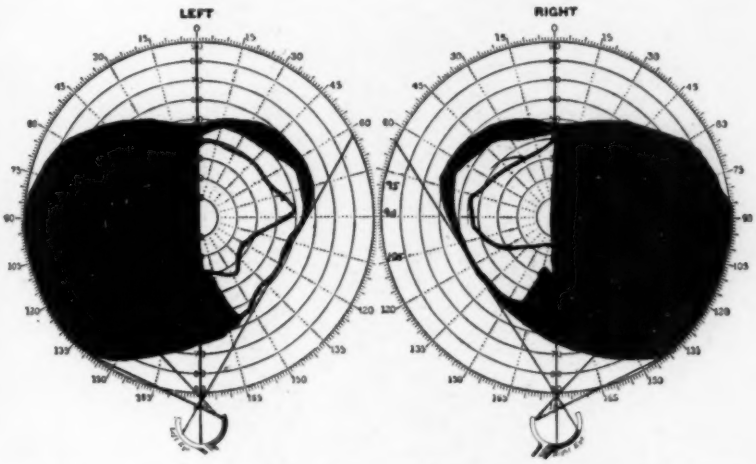


Fig 9 (case 3).—Fields show persistent hemianopia, three years after operation, but vision has improved from 2/60 in each eye to 20/30 in the left and 20/20 in the right eye.

sudden impairment in vision. She could see less well to the right than to the left, although vision was poor in all directions and everything appeared hazy. In August, she had her first attack of vomiting. She had had occasional attacks of dizziness; her eyes were more prominent than they were, and during the past year she had had diplopia at times.

Physical Examination.—The patient was well nourished, with no apparent pituitary stigmas. With the exception of a palpable thyroid, the general physical examination in all respects gave negative results.

Neurologic Examination.—Failed to detect any motor, sensory or reflex disturbance. With the exception of the optic, there was no lesion of the cranial nerves. The cerebrospinal fluid pressure was 14 mm. of mercury.

Pituitary Signs.—The basal metabolic rate was minus 4.8.

Ophthalmologic: Vision was: left eye, 2/60; right eye, 2/60. The disks showed a yellow, waxy atrophy, but the margins were well defined. There was a bitemporal hemianopia which was not present on Oct. 22, 1926; though there was still some vision in both upper temporal fields, there was marked contraction of each nasal field.

Roentgen Ray: The pituitary fossa measured: vertical, 4 mm.; anteroposterior, 10 mm. In October, the patient received fifteen roentgen treatments.

Operation.—On December 20, a transfrontal craniotomy was performed on the right under local anesthesia. A pituitary cyst was found and evacuated, and a considerable portion of the capsule removed. The wound was closed without

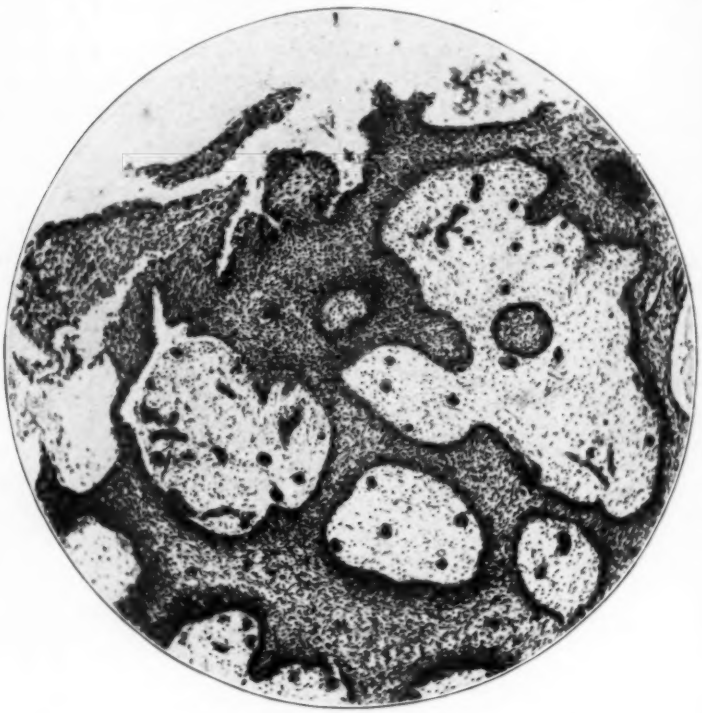


Fig. 10 (case 3).—Photomicrograph, low power, of adamantinoma.

drainage. Puncture of the anterior horn of the ventricle revealed fluid that was not under tension. The lesion was exposed as it presented in front of the chiasm. It appeared cystic, and a straw-colored fluid was withdrawn. A considerable portion of the capsule was removed; it appeared to be lined with a thin layer of adenomatous tissue. The cyst was approximately the size of an English walnut. What remained of the cavity was swabbed with a 5 per cent solution of iodine, and a small muscle graft was laid on the floor to control oozing.

Pathologic Diagnosis.—The diagnosis was adamantinoma (figs. 10 and 11).

Immediate Result.—Operative recovery occurred. Convalescence was uneventful.

Subsequent History.—Following the operation there had been some accession in weight and the amenorrhea had persisted. However, the patient, was not as

drowsy as she had been and stated that during the past month she was more like herself than she had been at any time since the onset of the illness. The nasal fields had been restored and there was some contraction of the temporal fields. Vision now was: left eye, 20/30; right, eye, 20/20, as compared with 2/60 in each eye before operation. She had fully regained her strength.

Comment.—This case has been selected as representing one of the series of adamantinomas. Apart from the amenorrhea, there were no pituitary stigmas except perhaps a tendency to drowsiness and lack of vigor. In this case, as in not a few others, vertigo was complained

Fig. 11 (case 3).—Photomicrograph, high power, of adamantinoma.

of (I shall speak of that later). In the postoperative period, in this as in many other instances, polyuria and polydipsia were observed, beginning immediately after the operation and often continuing for months. The headache in this case was of the pituitary type and not due to increased intracranial pressure, as determined by ventricular puncture at operation.

This case was the exception to the rule that in most cases of adamantinoma the patient is in the first or second decade. The age of this patient was 33. For the tumor of the pharyngeal duct two sites have been described, an upper group on the anterior aspect of

the infundibulum and a lower group between the infundibulum and the anterior lobe. As the sella turcica was not enlarged in this case, I assumed that the tumor occupied the upper of the two sites. The adamantinoma is one of three types of epithelial tumors taking origin from the hypophyseal duct, of which only sixty have been reported. Of these three—the papillary cyst, the spindle cell carcinoma and the adamantinoma—the latter is the most common.

Disturbance of sexual function, amenorrhea in the female and impotence in the male, is undoubtedly the most constant symptom in all pituitary syndromes; in my series, it occurred in 80 per cent. The question has been agitated as to whether sexual disturbances in pituitary lesions are due to a reflex action on the sex organs or to some inhibition on the pituitary itself. In a recent research, Sondek [3] came to the conclusion that the primary sex hormone resided in the pituitary and the secondary hormone in the ovaries and gonads. In view of the almost constant sex phenomena in pituitary syndromes, one is inclined to lean favorably toward this hypothesis.

CASE 4.—*A married woman, aged 40, childless, for fourteen years had amenorrhea as the only sign of pituitary dysfunction, and numbness and pain in the forearms and hands as a neighborhood symptom. One year prior to admission, there appeared evidences of posterior fossa invasion, a staggering gait, impairment of hearing, numbness of the face and signs of pressure including headache, vomiting and choked disk. The lesion proves to be of enormous proportions, an adenocarcinoma, invading the ethmoid and sphenoid sinuses, basilar process, nasopharynx and petrous bone, and extending through the incisura to the foramen magnum. Pathologic diagnosis: adenocarcinoma.*

History.—A woman, aged 40, was referred to the neurosurgical service of the University Hospital by Dr. Charles D. Post, of Syracuse, on Oct. 23, 1925. The patient's three brothers were living and well; one sister died of peritonitis and the father of nephritis. The mother had a gastric ulcer. As a child she had whooping cough, measles and chickenpox, and later influenza, pneumonia and pleurisy. She married when 21 years of age, but there had been no pregnancies. Regular periods had occurred from the thirteenth to the twenty-sixth year. Since then (1911) there had been amenorrhea. In 1911, there occurred cessation of menstruation, which up to that time had been regular. Simultaneously, there developed a feeling of numbness in both hands and forearms, associated with a dull aching pain. These symptoms were so intense and disturbing as to wake her up at night. The numbness of the fingers and night attacks of agonizing pain continued at intervals from 1911 to 1924, the year before she reported to the clinic. In January, 1924, she first experienced a dull ache in the right eyeball and a sense of protrusion. On combing her hair, there was a sense of numbness on the right side of the head. Coincidentally, she developed an intense fronto-occipital headache and was bedridden for four weeks. At this time, what she described as a "hard rolling sensation" in the head was almost constant and annoying. In October, 1924, there occurred impairment of hearing; in June, 1925, vomiting; on Oct. 19, 1925, vision became impaired. At this time, she was unable to walk without support.

3. Sondek: Med. Klin. **23**:463, 1927.

Physical Examination.—The patient was a white woman, about 40 years of age. No abnormalities were found in the lungs, heart or abdomen. The peripheral vessels were slightly sclerotic. The blood pressure was 118 systolic and 80 diastolic.

Neurologic Status.—The mental processes were rather slow and memory was somewhat impaired. She was quite garrulous, but cooperated well. Her station was unsteady; the Romberg sign was increased and in the heel-to-heel test she deviated to the right. Adiadokokinesis was present on the left. Sensation was not disturbed; there was no astereognosis; there were no paralyses of movement (dynamometer right and left, 100).

Cranial Nerves: The cranial nerves showed: II, see ophthalmic report; III narrowing of the right palpebral fissure; V marked hypesthesia on the right

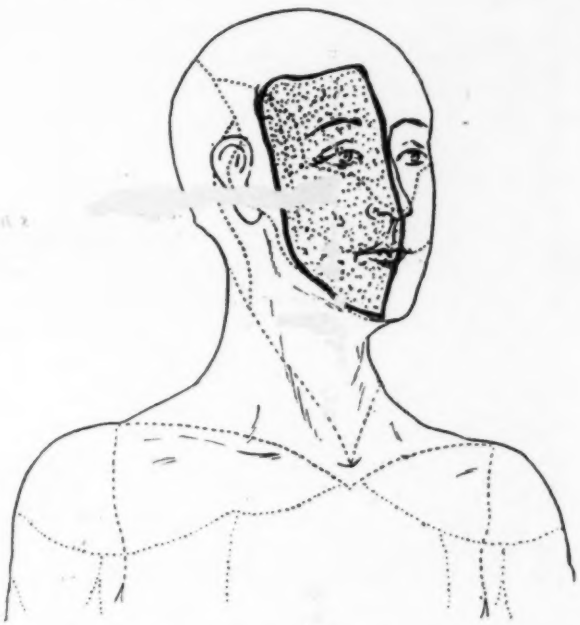


Fig. 12 (case 4).—Hypesthesia in the right trigeminal zone from invasion of the gasserian ganglion.

(fig. 12); VII slight asymmetry in repose on the right; VIII total deafness on the right; XI palatal reflex decreased on both sides.

Bárány Reaction: This pointed to a lesion of the right cerebellopontile angle, with pressure against the brain stem.

Roentgen Report: The dorsum sellae was still intact. The sella turcica measured: vertical, 20 mm.; anteroposterior, 24.5 mm. (fig. 13).

Ophthalmic Report: Outward rotation was limited in the right eye. Horizontal nystagmus was present on lateral rotation; vertical nystagmus on rotation upward. In both eyes the media were clear, the disks hyperemic; papilledema measured plus 3.5 diopters. The veins were engorged and tortuous; the arteries were reduced. No hemorrhages or exudates were present (fig. 14).

Cerebrospinal Pressure: The pressure was 28 mm. of mercury.

First Operation.—On Nov. 9, 1925, a suboccipital craniectomy in the first stage was performed. The operation was not without difficulties. The skull was exceptionally thick and of ivory density. After ligation of the occipital sinus the dura was divided sufficiently downward to decompress the medulla. The intracranial pressure, which was extreme, subsided on ventricular tap. After control of hemorrhage, further exploration was discontinued and the wound was closed.

The patient's convalescence was satisfactory. Her condition was improved by the decompression and, except for an occasional headache, she felt comfortable. She was no longer bedridden. In the interval between the operations she developed an attack of follicular tonsillitis.

Second Operation.—The second stage of a suboccipital craniectomy was performed on December 2, under local anesthesia. A tumor was found and sub-

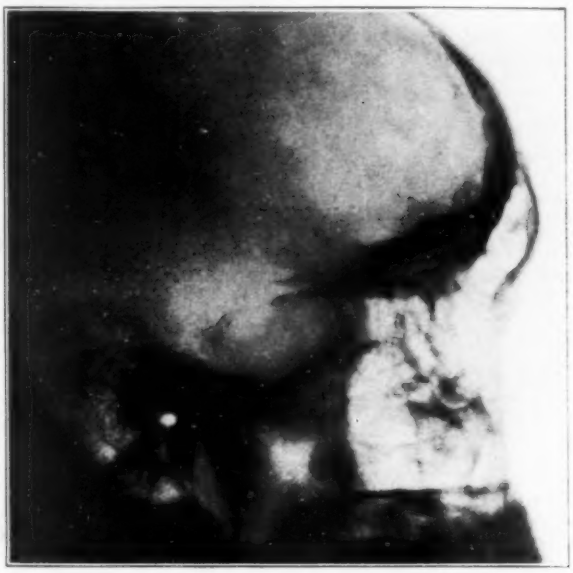


Fig. 13 (case 4).—Enormously enlarged sella turcica, with obliteration of the sphenoid sinus.

capsular evacuation was performed. A ventricular puncture was done on the right. As soon as the original incision for this operation was opened the cerebrospinal fluid escaped in large quantities. Beneath the aponeurosis, at the site of the original operation, there was also a collection of a considerable amount of fluid, so that after the dura was reflected all tension had been relieved and the subsequent steps of the operation were continued without difficulty. On opening the dura and elevating the right cerebellar hemisphere, there was no difficulty in seeing the tumor, as it presented in the angle between the pons and the cerebellum. The capsule was incised, and the contents of the tumor were removed fragmentarily. Grossly, the tumor had the appearance of a pituitary adenoma and this suspicion seemed to be confirmed by study of frozen sections. An effort was made to isolate the capsule and extirpate the growth completely. This, however, proved impossible. The cavity of the capsule was swabbed with Zenker's fluid and the wound closed in tier sutures.

Postoperative Course.—On the day after the operation, the patient's temperature rose to 106 F., and there were signs of pulmonary edema. The pulse and respiration were undisturbed. Hyperpyrexia continued during the day, but the edema of the lungs and excessive secretions in the upper air passages continued. An attempt to control these with ice packs and atropine failed, and the patient died thirty-six hours after the operation.

Autopsy.—On December 4, when the skull was opened, a firm bulging mass was seen, about the size of a walnut, presenting between the optic nerves and the chiasm. The tumor mass extended under the dura to the region of the right gasserian ganglion, invaded the sphenoid and ethmoid sinuses, penetrated the right foramen rotundum and extended into the nasopharynx. The petrous portion of the temporal bone was infiltrated and the tumor had completely surrounded the cavernous sinus. The basilar bone and the posterior clinoid processes, as well as the dorsum sellae, were completely eroded. The tumor had extended into the posterior fossa as far back as the foramen magnum.

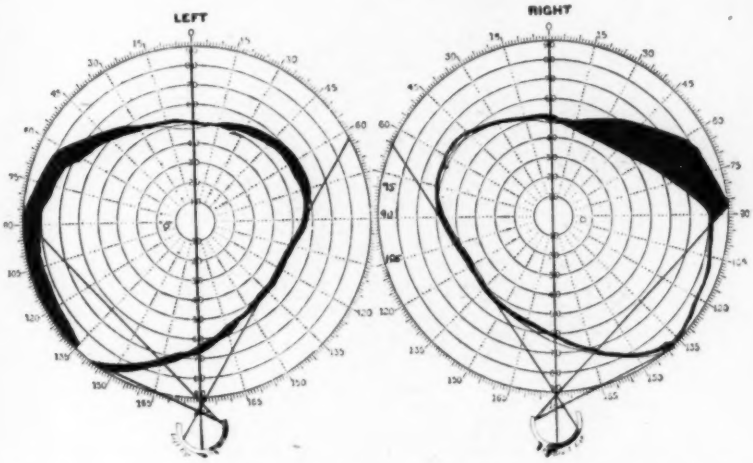


Fig. 14 (case 4).—Patient with an enormous pituitary tumor, but without field distortion; Oct. 26, 1925. Vision: right eye, 6/12; left eye, 6/9.

There was no evidence of hemorrhage in the posterior fossa. The structures of the brain, especially the peduncles and the pons and upper medulla, were greatly distorted and displaced toward the left. There was displacement of the cerebellar hemispheres so that the left hemisphere had been rotated backward and to the right.

The tumor was soft and gelatinous and encapsulated in its intradural aspect, but the capsule was not definable in the bony ramifications.

Microscopic Diagnosis: The diagnosis was adenocarcinoma (fig. 15).

Comment.—This case might be discussed with interest from various angles but it was selected particularly as illustrating the possibility of a primary pituitary lesion extending into the posterior fossa, with exhibition of symptoms of both pituitary and cerebellar dysfunction. Obviously, in this particular case, the tumor from every angle, as deter-

mined at autopsy, was inoperable because of its widespread extensions. Without exact knowledge as to the many ramifications of the lesion, when confronted with a similar clinical picture one would be tempted to explore first the posterior fossa. The patient's discomfort and disability were undoubtedly due to the posterior fossa extension. Incidentally, it may be noted that before the operation it was realized that there was a lesion of both the pituitary and the cerebellar fossae; that the lesion of the posterior fossa had originated in the pituitary fossa was not appreciated.

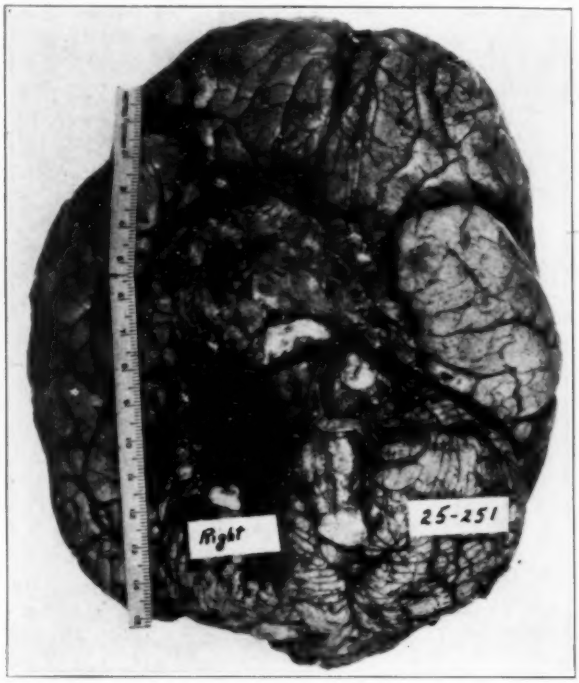


Fig. 15 (case 4).—Photograph of brain, showing enormous adenocarcinoma of the pituitary body. The extension into the posterior fossa had been removed.

Glancing at the chronologic sequence of events, it appears that the first symptoms observed were amenorrhea, numbness and pain in the hands. These appeared fourteen years before the patient was first seen, and at that time amenorrhea alone gave the clue to the pituitary involvement. Throughout these fourteen years there were practically no other symptoms, and then impairment of hearing and pressure phenomena (headache, vomiting and impairment of vision) made their appearance. The last to appear were the signs of cerebellar dysfunction.

The association of cerebellar symptoms with pituitary lesions has been observed before. In a number of our clinical records, vertigo is

frequently mentioned and this may be attributed to disturbance of the vestibular apparatus from hypertension alone. Disturbance of the equilibratory apparatus in this case obviously was due to the extension of the tumor into the cerebellopontile angle. In other instances it may be due to the pressure consequent on a secondary internal hydrocephalus. Just as an internal hydrocephalus secondary to an angle tumor may cause pituitary symptoms, so an internal hydrocephalus consequent on the extension upward of a primary pituitary lesion may cause cerebellar dysfunction (fig. 16). The sequence of events, to which symptom priority is given, will determine whether the primary lesion is pituitary or cerebellar. In case 4, the x-ray picture alone, with the enormous expansion of the sella, served as a discriminating sign. In some instances, as Bailey[4] has pointed out, the cerebellar symptoms

Fig. 16 (case 4).—Sketch of the relationship of the suprasellar region to the third ventricle. A shoebutton extension from a pituitary tumor causes complete obliteration of the third ventricle, an internal hydrocephalus and all the signs of increased intracranial pressure.

may be due to interruption of some cerebrocerebellar connection. The fatality in this case seemed to be due to a vasomotor phenomenon, characterized by excessive secretion throughout the upper air passages and lungs. The pulse and respiration were at first undisturbed. The function of the vasomotor center may have been consequent on an edema, following the relief from pressure. At autopsy, the operative field was bloodless.

CASE 5.—*A youth, aged 19, within ten months of the first evidence of an intracranial lesion became totally blind. The removal of a large pituitary adenoma*

4. Bailey, Percival: Concerning the Cerebellar Symptoms Produced by Suprasellar Tumors, Arch. Neurol. & Psychiat. **11**:137 (Feb.) 1924.

relieved the headache. The administration of pituitary and thyroid extracts transformed a somnolent, lethargic, helpless subject into one physically active and mentally alert.

History.—A boy, aged 19, was admitted to the neurosurgical service of the University Hospital on Nov. 3, 1925, having been referred by Dr. J. P. Roebuck. He had had measles when a child, but no other children's diseases. In 1922, he had a genital sore, but never had urethritis. His mother, father, six brothers and three sisters were living and well. There were no endocrine disturbances in other members of the family.

In March, 1925, the patient was knocked unconscious by an iron handle which flew off a vise. He returned to work the following morning. In May, he began to have a dull throbbing headache, chiefly in the left frontal region, lasting from five to thirty minutes, and at about the same time he noticed that this vision began to fail. Then followed diplopia and attacks of projectile vomiting. The headaches were often worse at night and would waken him from sound sleep. In July, he became totally blind.

Neurologic Status.—The patient's mental reactions were very slow. He appeared definitely subnormal. There were no signs of cerebral or cerebellar dysfunction, save mental apathy. Of the cranial nerves, the sense of smell was lost on both right and left sides. The patient presented many of the stigmas of pituitary dysfunction, chiefly of the Fröhlich syndrome, including excessive deposits of fat and accession in weight. In nine months his weight increased from 125 to 165 pounds (56.7 to 74.8 Kg.). The fingers were tapering; there was a resemblance of second incisor and canine teeth; the texture of the skin was smooth; there was no hair on the face or in the axilla; the pubic hair line was of feminine type. The patient slept most of the time. The cerebrospinal fluid pressure was 20 mm. of mercury. The Wassermann reaction was negative. The basal metabolic rate was minus 29.

Roentgen Report.—There were marked enlargement of the pituitary fossa and atrophy of the dorsum sellae and posterior clinoid processes. The right ethmoid and left and right sphenoid sinuses were cloudy.

Ophthalmic Report.—On November 5, the left eye was hyperopic plus 2.5 diopters and the right eye, plus 3 diopters. The disks showed subsiding papilledema, with atrophy. The arteries were reduced in caliber. There were no hemorrhages or exudates. There was total blindness.

Diagnosis.—From the roentgen studies and the pituitary stigmas it seemed apparent that I was dealing with an intrasellar pituitary lesion, and while the patient was totally blind at the time it was hoped, because of the apparently short duration of the lesion, that light perception or vision for large objects might be restored by the relief from pressure.

Operation.—On November 25, a transfrontal craniotomy was performed on the right under local anesthesia, and a flap reflected. The dura was tense. A ventricular tap was made, with evacuation of half a test tube of fluid and relief from tension. The right olfactory bulb was divided. A cyst was exposed and yellow fluid withdrawn. The capsule was incised and the contents of the cavity removed with a curet, together with a considerable portion of the capsular wall, including a small protuberant mass which had almost completely enveloped the left optic nerve. The cavity was swabbed with iodine and the wound closed. The patient's condition throughout the operation was gratifying. The blood pressure was maintained, and the pulse was extraordinarily slow.

Pathologic Diagnosis.—The diagnosis was adenoma.

Immediate Result.—Recovery took place. Following an uneventful convalescence the patient was discharged from the hospital on December 17.

Readmission.—On Nov. 19, 1926, about one year after the operation, the patient returned for a course of postoperative irradiation. His condition had not improved since discharge save that the headaches were not so severe. A reexamination failed to reveal any additional symptoms save fine tremors at times in both upper and lower extremities. Cerebration was slower than a year before and he slept most

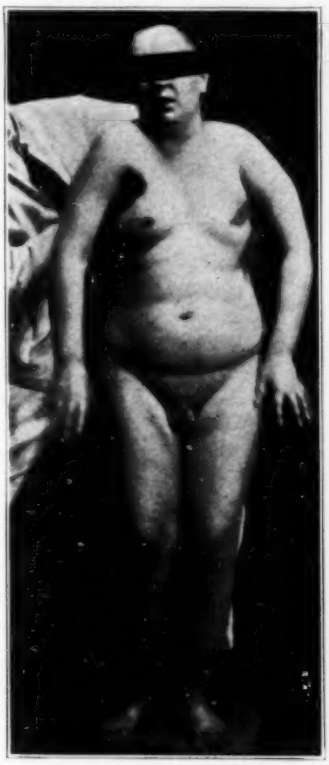


Fig. 17 (case 5).—Photograph of patient shortly after the inauguration of glandular therapy (thyroid and pituitary extracts).

of the time. On December 21, he was gradually becoming more comatose and was difficult to arouse. The cerebrospinal pressure was now 30 mm. of mercury, as compared with 20 on the first admission.

On Jan. 1, 1927, pituitary feedings of both anterior and posterior lobe, 2 grains (0.130 Gm.) night and morning, were instituted (fig. 17). On February 20, from a somnolent, almost comatose state the patient had become alert and able to get out of bed into a wheel chair. On March 1, thyroid extract, 1 grain (0.065 Gm.) daily, was started. On March 10, the cerebrospinal pressure was 12 mm. of mercury. On March 14, the patient's condition had improved so much that he was allowed to leave the hospital with instructions to continue glandular therapy.

Readmission.—At the time of his last discharge, he could hardly walk. On August 25, he was able to get about unaided, and his somnolence had entirely disappeared. Six weeks before, he had his first nocturnal emission, and since that time these had recurred, and erections were frequent. His weight now was 197 pounds (89.4 Kg.), a gain of 30 pounds (13.6 Kg.) since admission and of 72 pounds (32.7 Kg.) since the onset of the disease. The basal metabolic rate was now plus 9. He received 1 grain (0.065 Gm.) each of anterior and posterior lobe and of thyroid extract twice a day. On August 28, he was discharged (fig. 18).

Fig. 18 (case 5).—Photograph of patient eight months after inauguration of glandular therapy showing the striking change in physical vigor and capacity.

Comment.—This case is included for review because of the striking effect of glandular therapy. There are other interesting features in the clinical history, notably the short duration of the symptoms. From the huge dimensions of the sella turcica it was apparent that the tumor must have been present many months, but whereas in the majority of cases there is a history of headache for years, there was in this case one for only eight months. Especially rapid, too, in this case was the deterioration of vision. In most instances of pituitary lesions impairment of vision is due to primary rather than secondary atrophy. In this

case the subsiding papilledema bespoke a general increase in intracranial pressure and a secondary post-papillitic atrophy. The relation of a pituitary tumor to the third ventricle readily accounts for a ventricular block. Internal hydrocephalus in pituitary lesions is the exception rather than the rule, whereas in tumors of the pharyngeal pouch the reverse is true.

Of especial interest in this case were the effects of glandular feeding. While the headaches had in large measure been relieved by the operation, somnolence (in this case the most conspicuous symptom of pituitary dysfunction) persisted. The patient slept at least twenty out of twenty-four hours. No doubt there had been atrophy or destruction of pituitary tissue and possibly occlusion of the duct. There were, therefore, very clear indications for glandular feeding and with comparatively small doses, not more than 2 grains (0.130 Gm.) of each lobe twice a day, the patient's condition was transformed. From an inert mass of human flesh, he became physically and mentally alert, and his somnolence gradually disappeared. Not only that, but for the first time in the patient's life the assertion of sex function was observed, and with it the metabolic rate rose from minus 29 to plus 9.

My experience with pituitary dysfunction without evidence of a pituitary tumor has been limited. In fact, in but one case were the results from the administration of the whole gland very definite. Many years ago, after transsphenoidal operations, I administered pituitary extract to prevent recurrences, having in mind a possible analogy between thyroid feeding and pituitary feeding. But in no instance was there any reason to believe that the treatment had any inhibitive effect. Certain it is that the oral administration of pituitary extract has limitations in striking contrast to the oral administration of thyroid extract. One may be encouraged, however, by the recent work of Evans who, by the intraperitoneal injections of a pituitary extract prepared in his own laboratory, strikingly affected the growth and physical development of his experimental animal. A standardized preparation of pituitary extract for hypodermic administration may revolutionize the attitude toward glandular therapy. In my entire tumor series I have but three instances in which there was demonstrable improvement attending the oral administration of pituitary and thyroid extracts; one of these is the case under discussion; the second, a calcified adenoma in a middle-aged woman, and the third a patient with pituitary dysfunction without tumor. In two cases, somnolence with subnormal basal metabolism were conspicuous symptoms. In all three the improvement was striking. Thyroid extract in my experience is an effective supplementary agent as one might expect, since experimentally the interrelationship between the thyroid and the pituitary has been conclusively proved.

CASE 6.—*A woman, aged 31, married but childless, had an exceptionally short history—amenorrhea, headache and visual disturbance of only one year's duration. Within an hour of the removal of an adenocarcinoma the temporal fields were restored; the menses were reestablished two years later. Seven years after the operation, vision is normal and the patient is in perfect health.*

History.—A woman, aged 31, was referred to the neurosurgical service of the University Hospital on Nov. 24, 1921, by Dr. William F. Mercer. Her father had died of heart trouble, her mother of nephritis; four brother and two sisters were living and well. There were no manifest endocrine disturbances in the family tree. The patient was married but had never been pregnant. Apart from the diseases of childhood, she had had malaria (1906) but no other illnesses. There had been no accidents or operations. In December, 1920, the menses, which prior to that time had been regular, ceased and had not since recurred. Coincidentally, she began to have severe headaches. The pain at first was confined to

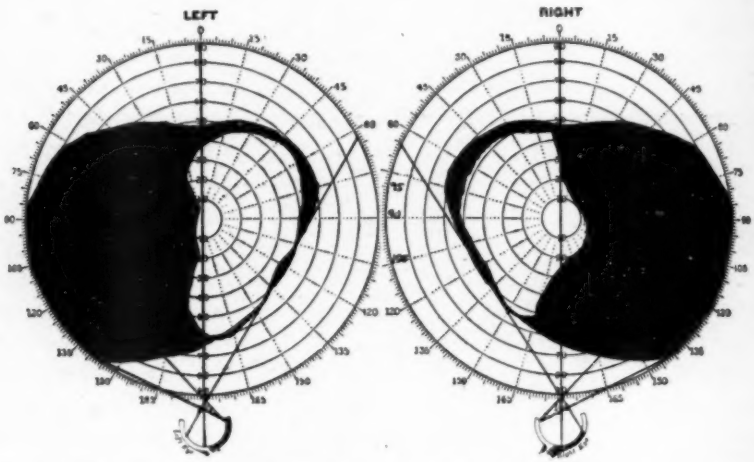


Fig. 19 (case 6).—The fields before operation, Nov. 28, 1921. Complete bitemporal hemianopia. Vision: right, 20/20; left eye, 20/200.

the right temple, but later spread all over the head. Lately, the headaches had been less severe, and for the past two months she had had none. Formerly, she had attacks of vomiting with the headaches, but not recently. In May, 1921, five months after the cessation of the menses, her vision began to fail, and she noticed lack of acuity on the left side of the left eye. This gradually grew worse and then the right eye became affected. There had been some accession in weight.

Physical Examination.—The patient was well nourished and well developed; the hands and feet were not out of proportion. There were no abnormality of gait or station and no disturbance of sensation or motion. The tendon reflexes were prompt and equal on the two sides. She had a slight enlargement of the thyroid gland.

Pituitary Signs.—Roentgen Report: The posterior clinoid processes had disappeared. There was not much encroachment on the sphenoid sinus; while measurements could not be made, there was manifest enlargement of the sella turcica.

Basal Metabolic Rate: The rate was minus 13.

Ophthalmic Report: The fields showed bitemporal hemianopia. The disks were slightly gray but well defined. The superficial capillarity was good and there were no fundus changes. Vision was: right eye, 20/20 and left eye, 20/200 (fig. 19).

Operation.—On Nov. 29, 1921, a transsphenoidal approach was made, with evacuation of a pituitary cyst, under ether anesthesia. The endopharyngeal method was used. The septum was resected submucously, the vomer removed and the

Fig. 20 (case 6).—Adenocarcinoma of the pituitary; × about 250. The nuclei average 7 microns (range from 5.8 to 11.7).

sphenoid sinus opened. The sphenoid sinus was of tremendous proportions and apparently had not been encrcached on by the floor of the sella. The floor of the sella had entirely disappeared so that the wall of the cyst presented. The capsule was split longitudinally and there immediately escaped a quantity of fluid. The cavity was curetted and a small quanity of tissue removed; the cavity was swabbed with saturated solution of tincture of iodine.

Pathologic Report.—The diagnosis was adenocarcinoma (figs. 20 and 21).

Immediate Result.—Operative recovery occurred. The patient was discharged on December 15.

Subsequent History.—Immediately after the operation, the temporal fields were entirely restored. During the course of the next two years the patient received

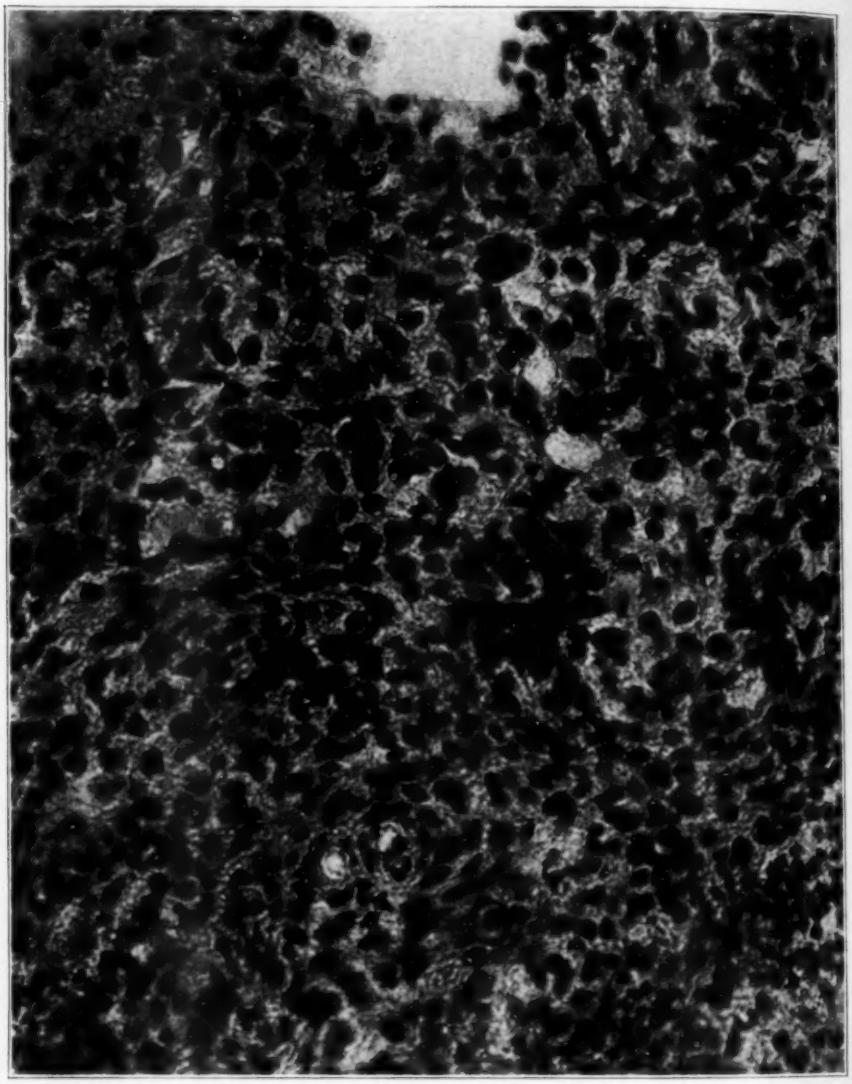


Fig. 21 (case 6).—Adenocarcinoma of the pituitary body; × about 700. The nuclei average 7 microns (range from 5.8 to 11.7).

five courses of irradiation. In June, 1924, three years after the operation, the patient's vision was: right and left eye, 6/5; the fields were normal (fig. 22). At the time of operation she weighed 126 pounds (57.2 Kg.); one year later, 145 pounds (65.8 Kg.), and three years later, 133 pounds (60.3 Kg.). In January,

1923, the menses were reestablished. The final report was received on Oct. 3, 1927, six years after the operation, at which time the fields and vision were perfect; the weight was 129 pounds (58.5 Kg.) (fig. 23).

Comment.—This clinical record has four points of interest: (1) in the character of the lesion; (2) in the comparatively short duration of the pressure symptoms; (3) in the immediate restoration of fields and (4) in the restoration of menstrual function. The first symptom of pituitary dysfunction, amenorrhea, appeared only eleven months before the operation, and the first sign of visual loss only six months. At this clinic this is an exceptional record. The effect of the operation on the fields was impressive. Within an hour of the operation, the temporal fields were entirely restored. Failure or success in restoring fields depends on whether the field distortion is due to pressure alone

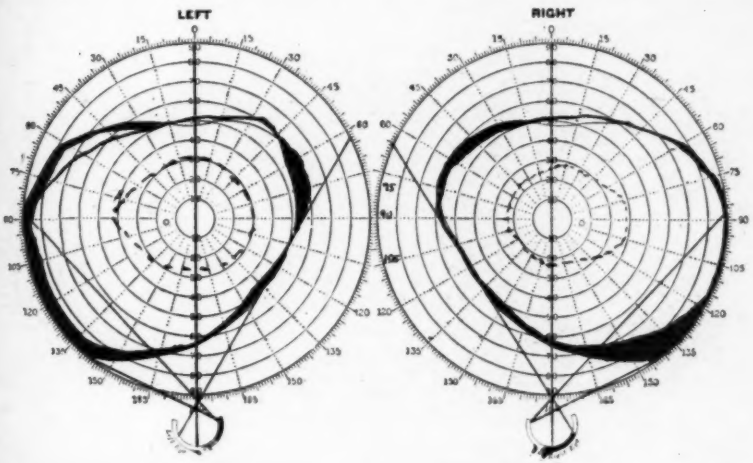


Fig. 22 (case 6).—The fields two and one-half years after a transsphenoidal evacuation of sella contents (compare with fig. 19). Vision: right eye, now 6/5, formerly 20/20; left eye, now 6/5, formerly 20/200 (June 2, 1924).

or to atrophy. In many instances, when vision in the nasal fields has been restored to normal, the temporal hemianopia may persist. The prognosis as to restoration of fields is related directly to the duration of the lesion. If atrophy is already established, obviously the field defect will persist.

The result of the operation is exceptional in that menses were reestablished. Often the first symptom to appear, antedating others frequently by many years, loss of menses is rarely affected by an operation, even though there has been a gratifying result in all other respects. In my experience the administration of ovarian extract has been without apparent influence.

The pathologic diagnosis in this case was adenocarcinoma. In my total series, adenocarcinoma was recorded in 12 per cent. The average age of the patients was 32 years, the oldest being 46 and the youngest, 18 years. It is not without interest to note that in this series, with the exception of sexual dysfunction, there was trivial evidence of posterior or anterior lobe insufficiency. Slight adiposity, polyuria or increased sugar tolerance alone are mentioned. In only one of the series was the adenocarcinoma grossly different from the adenoma. In this case the tumor was of large proportions and extended into the posterior fossa. I have no record of metastases. While the tumor is malignant pathologically, mere evacuation of the capsular contents seems sufficient to effect a permanent cure.

Fig. 23 (case 6).—Photograph of patient eight years after transsphenoidal evacuation of pituitary cyst.

Patients with pituitary lesions frequently exhibit a polyglandular syndrome. A small percentage of my cases, as in case 6, show moderate enlargement of the thyroid gland. The almost invariably subnormal metabolic rate may well be attributed to thyroid insufficiency. In two cases, active lactation was an associated symptom; in one I have seen precocity suggesting a pineal involvement; there are no instances of thymus enlargements. Sterility and amenorrhea are further evidences of polyglandular relationships. Of only five cases in the series without amenorrhea, in three the lesion was an adenocarcinoma. Accession in weight, another frequent physical characteristic in the pituitary subject, is often attributed to posterior lobe insufficiency. This, however, is by no means proved. Accession in weight may be due in part to a subnormal metabolism or in part to genital atrophy.

CASE 7.—*A man, aged 33, had had headaches for three years; failing vision in the left eye for one year and in the right eye for six months; recently, there had been herpes of the lower lip. Eight years after an evacuation of the cyst by the transsphenoidal route, the patient is in perfect health with no signs of recurring pressure or pituitary dysfunction.*

History.—A man, aged 33, single, was referred to the neurosurgical service of the University Hospital on April 5, 1921, by Dr. David Riesman and Dr. E. A. Sweeney. He had had the usual diseases of childhood, and influenza in 1918. There was no history of endocrine disturbance, malignant disease or tuberculosis in the family. In 1918, the patient began to have headaches, chiefly frontal and bilateral and as a rule associated with nausea and vomiting; at that time, he passed the physical examination for service in the U. S. Army, from which he was discharged apparently well in December, 1918. In the spring, 1919, the headaches recurred and were more severe in the left frontotemporal region. In April, 1920, vision of the left eye became blurred and within a few months he could not read with it. Recently, there had been blurring of vision in the right eye. Lately, the attacks of headache and vomiting had been so severe that he had been totally incapacitated, and he seemed to be unsually drowsy.

Neurologic Status.—There were no disturbances of sensation and no paralyses, but on standing there seemed to be a slight tendency to sway. The movements were not incoordinate. Of the cranial nerves, the second and fifth were involved. There was an herpetic eruption at the angle of the mouth and lower lip. The patellar tendon reflexes were present but not active. The achilles tendon reflexes were absent. The weight was 165 pounds (74.8 Kg.).

Pituitary Signs.—Drowsiness was present.

Roentgen Report: There was marked encroachment of the sella turcica on the sphenoid sinus, suggesting a large primary pituitary lesion.

Ophthalmic Examination: In the right eye, the disk was normal; there were no fundus changes. In the left eye there was practically complete optic atrophy. The fields on the right showed general contraction, which was more marked on the temporal side.

Operation.—On April 22, 1921, a transsphenoidal approach was made under ether anesthesia; the endopharyngeal method was used. What remained of the sphenoid sinus was opened and the thin shell-like floor of the sella removed, exposing a shiny capsule of bluish color. When the capsule was incised a quantity of yellow fluid escaped. The cavity was swabbed with tincture of iodine solution and after control of the bleeding with epinephrine tampons, the operation was concluded.

Immediate Result.—Recovery occurred.

Subsequent History.—Within a week of the patient's discharge, the hemianopia in the right eye, except for color, had disappeared. The patient had been seen or heard from at intervals since the operation, the last occasion being on Oct. 6, 1927, six and a half years after the operation. He had resumed his former occupation; he had gained 5 pounds (2.3 Kg.); his headaches had not returned; the field of the right eye was full; vision was 20/20 without glasses. The left eye, as before, was totally blind.

Comment.—The ultimate result in this case is extremely gratifying, especially in view of the fact that the operation fell far short of being a radical procedure. As no tissue was removed the pathologic diagnosis is undetermined, but one may assume that there was an adenoma

with cystic degeneration. The approach to the pituitary lesion by the transsphenoidal route, as in this case, permits of little but the evacuation of the contents, and in this instance this included only the fluid contents. The possibility of relapse is greater, therefore, than by the transfrontal attack. By the latter one can readily dissect the capsule free from the optic nerves and chiasm and remove a greater portion of the capsule. Often, as observed in the transfrontal operation, the tissue-lined capsule is so substantial and fixed that the evacuation of the fluid contents is not followed by collapse. One is surprised, therefore, with the permanency of the results that have followed the transsphenoidal operation, in which the relationship of the capsule to the optic nerves and chiasm has not been disturbed.

As in many, if not in the majority, of my cases, there is a decided difference in the visual disturbances of the right and the left eye. In

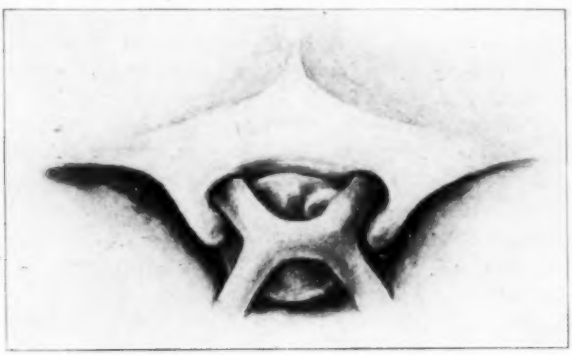


Fig. 24 (case 7).—Sketch of operative field, showing shoebutton protuberance of pituitary adenoma immediately against the right optic nerve.

the case under consideration, as in many others, the left eye became involved first, and vision in this eye was almost lost before the right eye was affected. This phenomenon is readily explained by the asymmetry of the lesion. I have noted, in explanation of the asymmetry of the visual defects, not infrequently, small shoebutton protuberances from the capsule in contact with one optic nerve or the other (fig. 24).

The effect of the pituitary lesion on the metabolic rate is a phase of the pathologic physiology that has been little discussed and never explained. I have seen the statement made, evidently on a theoretical basis, that in cases of hyperpituitarism the metabolic rate will be increased and in hypopituitarism decreased. My experience is not at all in accord with this belief. Quite the contrary. It is the exceptional case in which the metabolic rate is not subnormal. For example, in one series of thirty recorded observations the rate was plus in only three instances (plus 2, plus 6 and plus 11), all within normal limits.

Whereas, in many instances the rate varied from minus 15 to minus 35, and in one instance was minus 56. Naturally, one associates the function of the thyroid gland with the pituitary in this connection and no doubt there must be some inhibition of thyroid function to account for the lowered metabolic rate. While there were a number of instances in my 124 cases of primary pituitary lesions with an associated enlargement of the thyroid gland, I had but one instance of hyperthyroidism; in this case the metabolic rate was normal despite the fact that the patient exhibited, in addition to the pituitary picture, all the symptoms of a grave form of exophthalmic goiter. Is it possible that the effects of one of these lesions, the pituitary adenoma, may have offset the effects of the other, a hyperplastic thyroid?

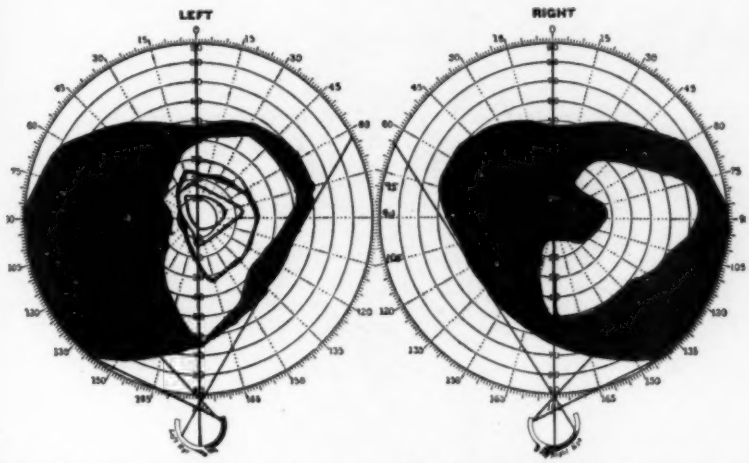


Fig. 25 (case 8).—Fields before transsphenoidal evacuation of sella contents, Oct. 22, 1914.

CASE 8.—*A middle-aged man, eleven years before admission, noted a loss of libido; nine years before failing vision in the right, and six years before failing vision in the left eye. Memory was impaired, and he had fits of depression, irritability and emotional upsets. With the exception of the latter, eleven years after the first operation (transsphenoidal decompression) and nine years after the second operation (transfrontal extirpation of a pituitary adenoma) vision is conserved and there are no signs of recurring endocrine disturbance.*

History.—A man, aged 42, was first admitted to the neurosurgical service of the University Hospital in November, 1914. He was referred by Dr. G. E. de Schweinitz. His sister and all of his mother's people were large. The patient, since school days, had worked on the railroad until he was promoted to the position of division superintendent. He was married, but had no children. In June, 1903, he was struck on the left side of the head by a heavy iron hook and was unconscious for three days. He evidently had sustained a fracture of the base of the skull with involvement of the seventh and eighth nerves. Shortly after the accident (1903), he noticed a reduction in libido, and three years before

examination (1911) became impotent. In 1905, nine years before examination, his vision began to fail, especially in the right eye, and in 1908 he began to lose the temporal field. After an interval of six years, six months before examination, he began to lose the temporal field in the left eye. During these eleven years, he had gained in weight from 150 to 210 pounds (68 to 95.2 Kg.). The past two years his memory had become somewhat impaired. He wore a size and a half larger shoe. He had a large bony frame and much panniculus adiposis.

Pituitary Signs.—The enlargement of the sella turcica, impotence and field distortions were the chief signs of a primary pituitary lesion. Dr. de Schweinitz reported a left lateral hemianopia, optic atrophy and two-thirds vision in the left eye. The right eye was almost blind (fig. 25).

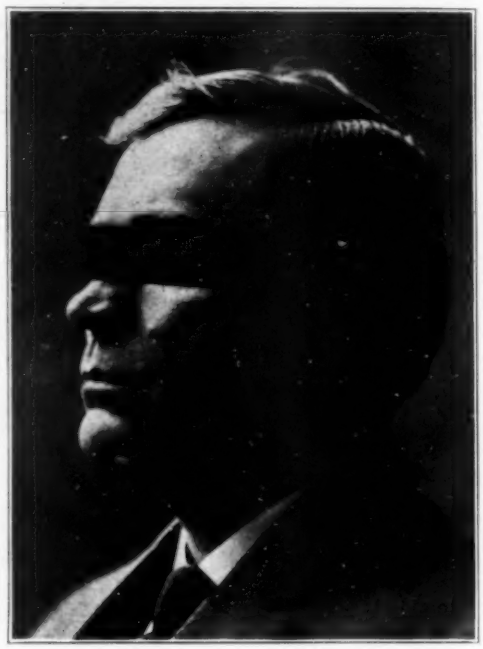


Fig. 26 (case 8).—Photograph of patient after transsphenoidal and before transfrontal operation.

Operation.—On Nov. 7, 1914, a transsphenoidal approach was made, with exposure of the tumor and partial removal of the contents.

Immediate Result.—Recovery took place (fig. 26).

Readmission.—On Oct. 25, 1916, following the first operation, vision in the left eye improved and the field enlarged. The patient lost 13 pounds (5.9 Kg.); he was more active and alert, with less headache. He had had, from the beginning of his illness, attacks of depression and irritability and lately occasional emotional upsets. About five weeks before examination, vision suddenly became worse and headaches had become more frequent. On reexamination, there were no physical signs of moment other than those previously noted. The blood pressure had dropped from 90 to 65. In the interval, the patient had received both pituitary and thyroid extract (fig. 27).

Second Operation.—On October 28, a transfrontal approach was made. The operation was performed in two stages. At the first, the cranial section was made and the wound closed. At the second (November 1), under ether anesthesia, the flap was reflected and the tumor exposed and removed fragmentarily. Practically the entire contents of the sella were evacuated.

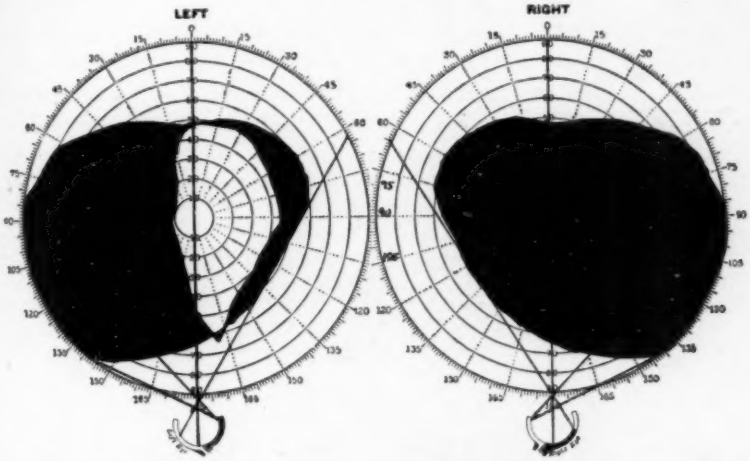


Fig. 27 (case 8).—Fields twenty-three months after transsphenoidal evacuation of sella contents and before operation by transfrontal route; Oct. 11, 1916.

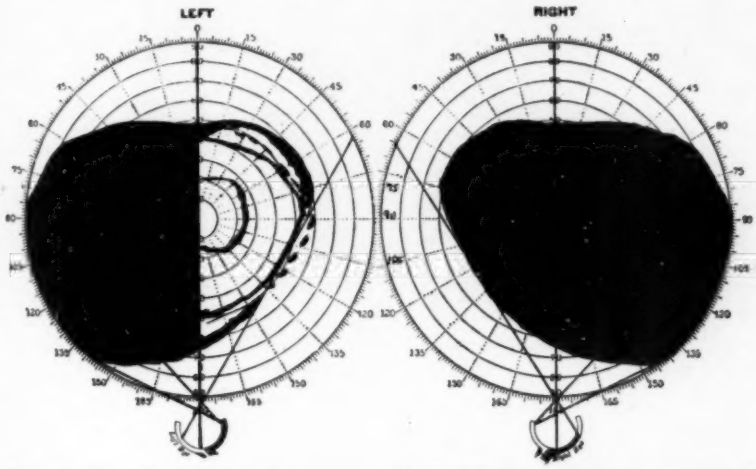


Fig. 28 (case 8).—The patient was practically blind in the right eye at the time of the first observation. There was total blindness in this eye preceding the second operation. Note how vision has been conserved in the nasal field of the left eye over a period of eleven years after the second operation, Nov. 2, 1927.

Immediate Result.—Recovery occurred.

Subsequent Course.—Since recovery from the last operation, the patient had been continuously employed. At one time he wrote that he felt so well that he would not know anything was the matter. He returned for reexamination on

Nov. 21, 1927, nine years after the last observation. The patient had not gained in weight. Headaches had practically disappeared; he still had attacks of irritability, depression and emotional upsets (figs. 28 and 29).

Comment.—I present this case because, with the exception of one other, this is the longest period of relief in my series. Thirteen years have elapsed since the first operation. Furthermore, the first symptom, loss of libido, was noted nine years prior to his first visit to the clinic. So that, in all, there is a pituitary history of twenty-two years' duration. The longest history of pituitary dysfunction in my series was in the

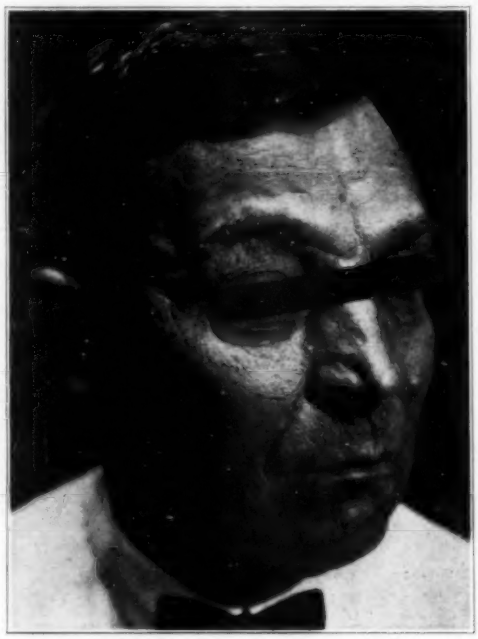


Fig. 29 (case 8).—Photograph of patient eleven years after evacuation of sella contents by transfrontal route.

case of a woman, aged 55, with a calcified adenoma, who had had amenorrhea for twenty-nine years.

Although the patient sustained a fracture of the base of the skull shortly before the onset of the illness, there is no evidence in my records to suggest any relationship between pituitary lesions and trauma. I know of no other case in the series in which attacks of depression, irritability and fits of crying were part of the picture. This irritability and emotional imbalance might suggest an associated thyroid disturbance, but at no time was there any enlargement of the thyroid gland.

This case illustrates further the possibility of relapse after the transsphenoidal method. I have, in several instances, had to operate

for relapses, and at the second operation have always employed the transfrontal approach. Were it not for the greater incidence of relapses after the transsphenoidal route, it would unquestionably be the method of election, not only because the hazards are fewer, but because the cosmetic results are ideal.

CASE 9.—*An adenoma without evidence of pituitary dysfunction; symptoms relieved by transfrontal extirpation.*

History.—A man, aged 29, was referred to the neurosurgical service of the University Hospital on Jan. 6, 1927, by Dr. Spiller and Dr. Siggins. Only three

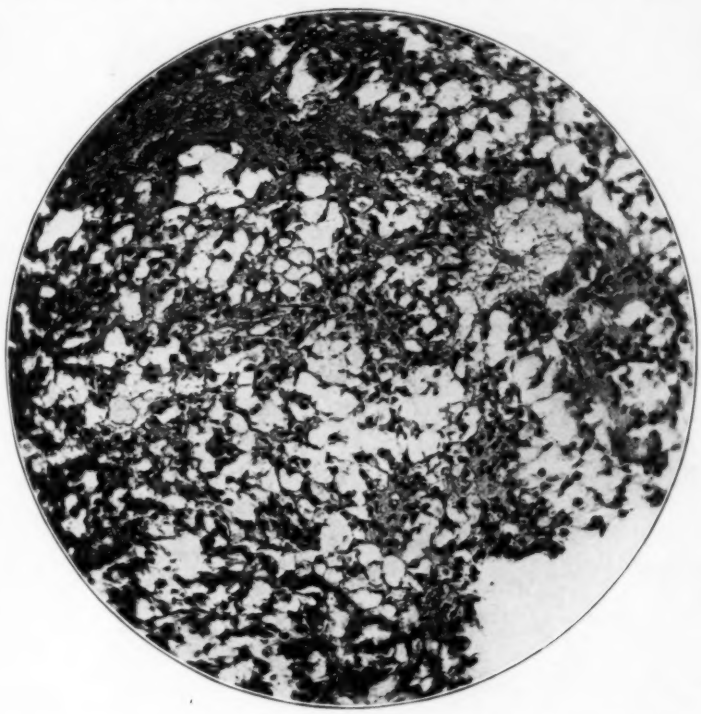


Fig. 30 (case 9).—Photomicrograph of a basophilic adenoma removed by operation.

months before, he first noticed blurring of vision in the right eye. With the left eye closed he could see very little and could not read with the right eye. It was not until two weeks before examination that the left eye became affected. When walking he noticed that he bumped into people and objects on both sides.

Physical Examination.—The patient was a well developed man of average height and weight, with no apparent lesion of the heart, lungs or abdomen. There was no disturbance of motion, sensation or tendon reflexes.

Ophthalmic Examination.—Bitemporal hemianopia was present. Vision was: right eye, only shadows; left eye, 6/7.5. The disks were waxy yellow.

Roentgen Examination.—There was marked depression of the pituitary floor. Accurate measurements were not possible because of atrophy of the dorsum sellae.

Basal Metabolic Rate.—The rate was minus 17.

Operation.—On Jan. 10, 1927, a transfrontal craniotomy was performed. A flap was reflected from the left temporofrontal region and the dura found to be under no tension. A horizontal incision was made in the dura, the frontal lobe being carefully protected with tapes and elevated. Two small veins running from the frontal to the falx were clipped. The lesion was readily seen pushing the optic

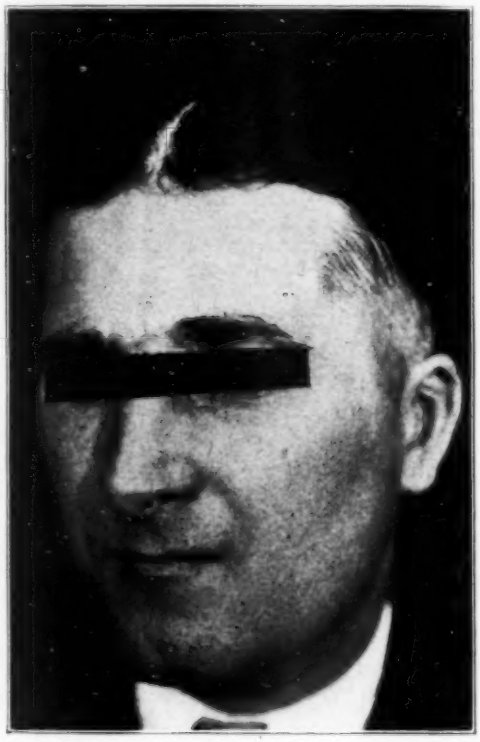


Fig. 31 (case 9).—The inconspicuous scar, six months after a transfrontal craniotomy.

nerves upward and outward so that they were flattened. With an aspirating needle, about 6 cc. of a brownish-red fluid was removed, and at once the tumor collapsed and pressure on the optic nerves was relieved. The anterior and superior walls of the capsule and that portion in contact with the left optic nerve and chiasm were freed, and a considerable portion of the wall of the cyst that presented in front of the chiasm was removed.

Pathologic Diagnosis.—The diagnosis was adenoma, basophilic (fig. 30).

Postoperative Course.—Apart from extreme thirst and a low respiratory rate on the night of the operation, the convalescence was uneventful and the patient was discharged on January 23, thirteen days after the operation.

Comment.—Following the operation, the patient received the usual course of irradiation and soon resumed his occupation (fig. 31). When last seen, an interval of twelve months, he had been working steadily and was generally symptom-free, with the exception of a moderate polydipsia. Vision in the left eye was 6/5; in the right eye, which before the operation was practically blind, 6/15. Neither field was entirely normal. That of the right eye was still hemianopic and in the left there was still a small quadrant defect.

This case illustrates a patient with a pituitary lesion of no small dimensions, without suggestion of a pituitary stigma. Though he was almost blind in the right eye before the operation, after the operation vision was 6/15.

The patient under discussion had an adenoma, the commonest of all pituitary lesions. In my series there were 76 per cent adenomas and 16 per cent adenocarcinomas. The average age at which the symptoms first appeared in the solid adenomas was 29 years and of the cystic adenomas 25 years. The average age at which the adenocarcinomas appeared was 33 years.

CASE 10.—*A girl in her teens, who had had six years' paroxysmal headaches, vertigo, visual hallucinations, epigastric pains and later visual defects, had an exceptionally large pituitary adenoma. To deal adequately with the lesion the operation was divided into stages with an interval of three months. At the first, the right portion of the tumor was removed; at the second, the left. Both operations were well tolerated, and the patient recovered with normal fields.*

History.—A girl, aged 17, was referred to the neurosurgical clinic of the University Hospital on June 26, 1927, through Dr. Baer of the Wills Eye Hospital. She had been well until 1921, six years before, when she began to have severe headaches, throbbing in character and referred to the supra-orbital region. These headaches at first lasted for a few hours or a day and then passed off, and were often associated with nausea and vomiting. Tinnitus in the right ear often appeared after the headache subsided and persisted for a while. Two months before the headaches began, she had a curious attack in which she thought she saw pictures of people appearing and disappearing on the wall. She heard no voices. These hallucinations lasted for a day or two and then vanished. She never saw bright light or scintillating scotomas. In January, 1926, vision began to fail; as the patient said, a film seemed to be growing over the eye from the temporal side. As time went on she complained of a sense of weakness in the knees and later of cramps, especially in the epigastric region. These pains were not related to the ingestion of food; at one time she had an attack of transitory blindness. All the while, the headaches continued with varying severity, mostly throbbing and frontal. Vomiting was occasional. At times she complained of vertigo; objects appeared to be turning around from left to right. Meanwhile, vision was becoming more and more impaired until she had another attack of transitory blindness, on this occasion in the left eye. The menstrual periods began in the sixteenth year; two periods occurred in each month, and were excessive and painful. Arrest of menses took place in April, 1927.

Physical Examination.—There was a palpable and symmetrically enlarged thyroid gland. The breasts were large for her age and recently had grown considerably in size. The hands and feet seemed disproportionately large for her age and race (colored). The reflexes were normal; there was no motor or sensory

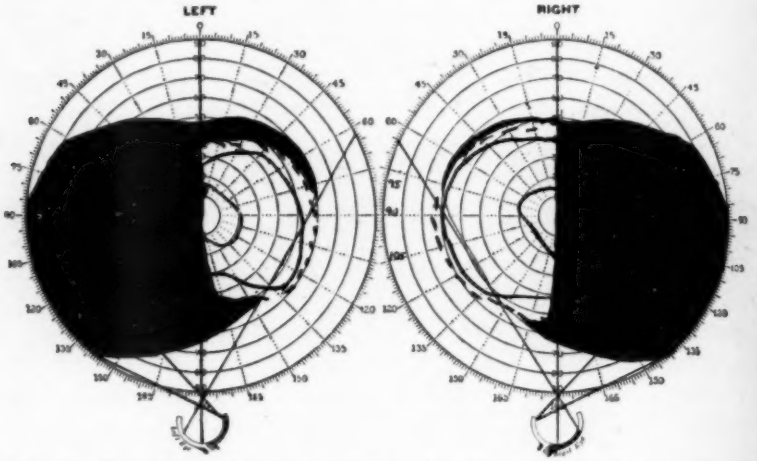


Fig. 32 (case 10).—Bitemporal hemianopia before operation, June 27, 1927. Vision: right eye, 6/6; left eye, 6/12.

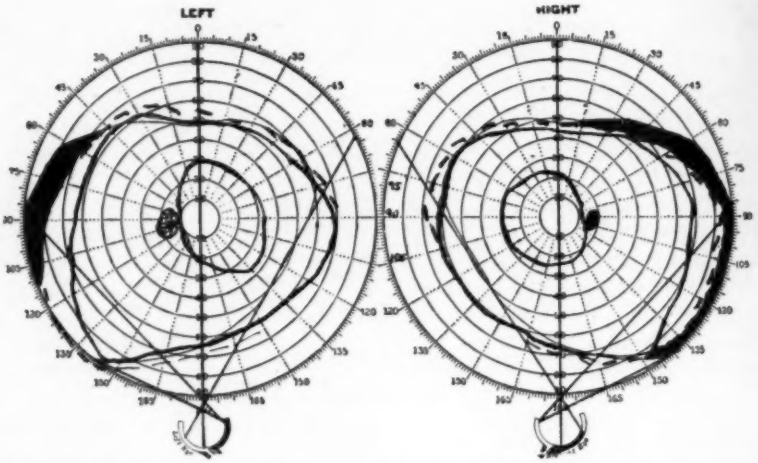


Fig. 33 (case 10).—Disappearance of hemianopia after bilateral craniotomy at two sittings, Oct. 11, 1927. Vision: right eye, 6/6; left eye, 6/9. Compare with figure 32.

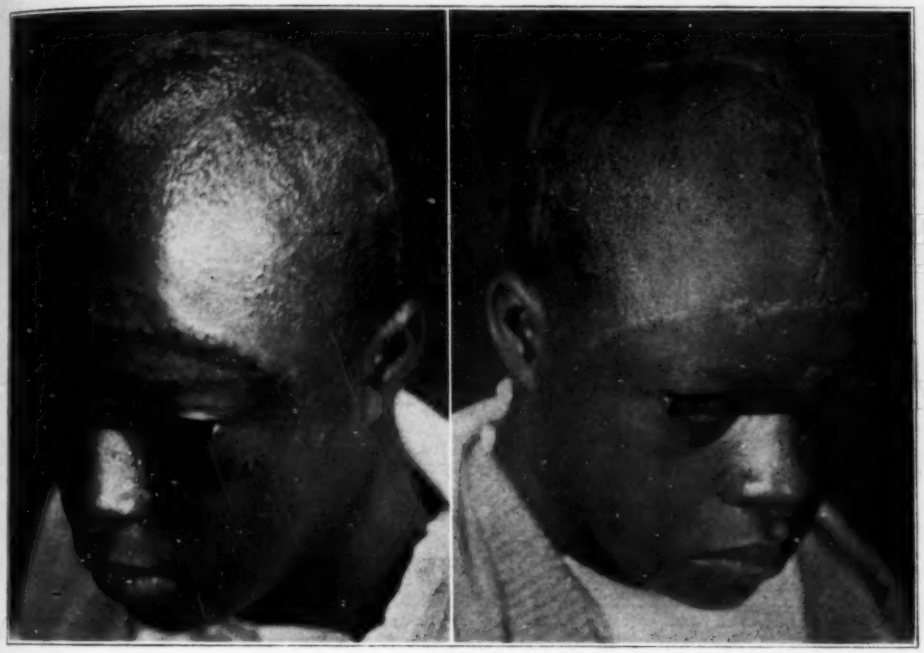
dysfunction; there was impairment of the sense of smell (left) and a right horizontal nystagmus.

Roentgen Report.—The pituitary fossa measured 22 by 16 mm. Atrophy of the dorsum sellae was present.

Pituitary Signs.—The basal metabolic rate was minus 20 per cent. The hands and feet were disproportionately large for her age. There was an accession of weight of 10 pounds (4.5 Kg.). Amenorrhea was present.

Ophthalmic Examination.—Bitemporal hemianopia was present. There was pallor of both disks, especially on the nasal sides, with a yellow waxy appearance. Vision was: right eye, 6/12; left eye, 6/6. There was a crossed diplopia and some divergence (fig. 32).

First Operation.—On July 1, 1927, a transfrontal craniotomy was performed on the right. There was considerable dural tension, but this was found to be due largely to a collection of fluid in the subarachnoid space, so that when the dura was opened and the fluid escaped in considerable quantity, the pressure subsided.



A B

Fig. 34 (case 10).—*A*, left craniotomy as the first stage of bilateral exposure. The flap in this case, for particular reasons, was higher than in my customary approach. *B*, a craniotomy on the right side, three months after that on the left.

The lesion was of unusually large proportions and the right optic nerve was displaced much farther out than in the average case. One cubic centimeter of bloody fluid was evacuated, and as much of the capsule as presented on the right side was removed. The tumor was of such dimensions that no attempt was made to deal with the lesion on the left side. During the operation, the blood pressure and pulse rate remained practically unchanged.

Immediate Result.—Operative recovery occurred, and the patient was discharged on July 11.

Readmission.—On September 27, since discharge, the patient had been free from symptoms. The menses returned in September for the first time since April. She drank from fourteen to sixteen glasses of water a day (polydipsia). Vision had improved and the fields showed definite retraction of the temporal fields, more marked on the right than on the left (see chart).

Second Operation.—On October 3, a transfrontal craniotomy was performed on the left, under local anesthesia. The dura was moderately tense and, as before, there was considerable fluid in the subarachnoid space. As much of the capsule as presented on the left side was removed together with the attached tissue, and the wound was closed.

Pathologic Diagnosis.—The diagnosis was pituitary adenoma (basophilic).

Immediate Result.—Operative recovery occurred, and the patient was discharged on October 14. Vision on discharge was: left eye, 6/6; right eye, 6/9. There was no obscuration of the temporal fields (fig. 33).

BLOOD PRESSURE CHART.

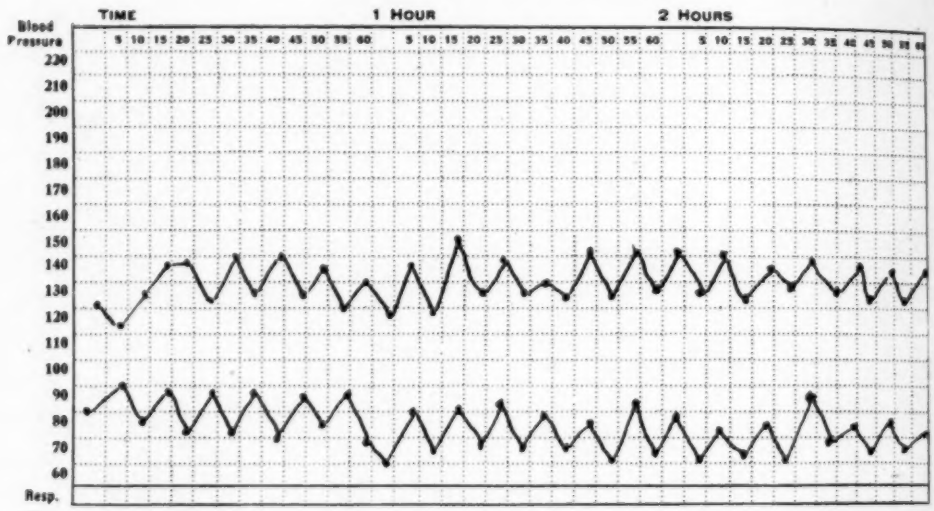


Fig. 35 (case 10).—The systolic and diastolic graph during a pituitary exposure under colonic anesthesia. Note the maintenance of the blood pressure throughout.

Comment.—As one reads in full the history of this patient, it corresponds in some respects to that of many other patients with primary pituitary lesions, except for a rather long period, six years, of headache and vomiting without signs of visual defect. There were, however, certain associated symptoms that are by no means common. The enlarged breasts suggested sexual precocity, possibly a pineal manifestation. There was also an enlargement of the thyroid gland, and these symptoms, with the amenorrhea, compose a polyglandular syndrome.

Attention is directed also to the group of symptoms that were related to the eighth nerve, the tinnitus and vertigo and the horizontal

nystagmus. But of exceptional interest to me were the visual hallucinations. In no other case of my pituitary series were these observed, and their occurrence here indicates the possibility of hallucinations as a sign of irritation of the chiasm as well as of the more central portions of the visual pathways. Unusual, too, and difficult to account for were the epigastric cramps. Taken altogether, the history and clinical manifestations were unique.

For the first time, in this case, the operative program was divided into two stages. The lesion was unusually broad and as it seemed impossible to deal with the left portion of the tumor from the original right-sided approach, no attempt was made to remove the left half of the tumor at the first sitting. The operative program, therefore, was divided deliberately into two stages, and after an interval of three months a second craniotomy on the right side was performed, and, as might have been anticipated, the maximum improvement was not obtained until after the second stage. The propriety of the bilateral operation may be questioned, but if this case may be used as a criterion it might seem to be justified not only by the immediate results but also by the end-results (fig. 34). Striking at both operations on this girl was the steadiness of pulse rate and blood pressure throughout. This I mention particularly because there is but one major hazard in the transfrontal operation, a hazard not common to other intracranial procedures—the hazard of what one may term pituitary shock (fig. 35). Occasionally, possibly half a dozen times, in my operative experience in an operation apparently uncomplicated, entirely devoid of any obvious difficulty, there may develop, perhaps at the conclusion of the operation or soon after, a decisive fall in the systolic blood pressure with marked acceleration of pulse. Appropriate remedies, especially solution of pituitary, epinephrine and ephedrine, may be given to raise the blood pressure, but all without effect. Nothing in my experience raises the blood pressure for more than a few moments and in from twenty-four to forty-eight hours the patient shows signs of collapse and dies. I called the picture "pituitary shock" merely to relate the clinical picture to the pituitary operation, but I have had the impression wholly without any demonstrable proof that the complication is in some way due to undue pressure on the suprasellar structures, so that it is now my established technic to approach the sella turcica from the side, that is, along the greater wing of the sphenoid. By this lateral approach, rather than from more directly in front, the brain elevator does not encroach on structures above the sella and undue trauma thereon is avoided. Hence, to revert to the case under discussion, when dealing with a lesion to avoid harmful pressure on these structures, the bilateral two-stage operation is safer. Let it be understood that this applies only to lesions of unusual dimensions and is not recommended as a routine procedure.

ACUTE, TOXIC (NONSUPPURATIVE) ENCEPHALITIS IN CHILDREN

A CLINICOPATHOLOGIC STUDY OF FIVE CASES *

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In the present study are recorded the clinicopathologic observations in five cases which may generally be classified as acute, toxic, nonsuppurative encephalitis. The first three cases presented a rather unusual, though characteristic pathologic picture in the form of acute and peracute processes of liquefaction. In the last two cases, the pathologic changes were less characteristic and corresponded largely with the condition ordinarily described in toxic, noninflammatory lesions of the brain. The clinical features in cases 1 and 4 were discussed by Beverly,[1] who, however, did not give a detailed pathologic description.

Nonsuppurative encephalitis has been known to occur: (1) as hemorrhagic encephalitis of the Struempell and Leichtenstern [2] type; (2) as postinfectious encephalitis, a sequel both to the exanthematous diseases and to influenza, as described by Oppenheim,[3] Abt [4] and others; (3) as epidemic encephalitis. But in recent years, a series of cases has been reported by various workers which, corresponding with none of the older classifications, seemed to constitute a heretofore not observed type of encephalitis in children. Anderson [5] was the first to describe cases of this order and was soon followed by Brown and Symmers,[6]

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* From the Division of Neuropathology (Dr. Hassin) of the pathology laboratories of the Research and Educational Hospitals of the University of Illinois, College of Medicine and the Children's Memorial Hospital (Dr. Brenneman).

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4. Abt. J. A.: Acute Nonsuppurative Encephalitis in Children, J. A. M. A. **47**:1148 (Oct. 13) 1906.

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6. Brown, C. L., and Symmers, D.: Acute Serous Encephalitis, Am. J. Dis. Child. **29**:174 (Feb.) 1925.

Stooss,[7] Grinker and Stone [8] and Brain, Hunter and Turnbull.[9] Kemkes and Saenger,[10] in a series of seventy-two cases, listed twelve as epidemic encephalitis, ten as postinfectious encephalitis, seventeen as questionable cases of epidemic encephalitis and thirty-three as etiologically not clear. Whether or not Marsh's [11] four cases, reported in 1910, belong to this new group is doubtful, as both his clinical and pathologic descriptions are too vague to permit a definite classification.

REPORT OF CASES

CASE 1.—*History.*—A white boy, aged 2 years and 9 months, was admitted to the Children's Memorial Hospital on Aug. 13, 1925. He had been well until ten hours before admisision, when he developed high fever, severe diarrhea, convulsions and coma. The mother and two other children developed diarrhea and fever on the same day. The personal and family history otherwise was essentially without significance.

Examination and Course.—On admission, the patient was comatose and appeared very ill. The jaws were closed so tightly that the throat could not be seen. There were irregular jerkings and changing movements of the eyes. The right pupil was larger than the left. The neck was not rigid. The chest and abdomen were normal. There was a bilateral Babinski sign. Death occurred on Aug. 14, 1925.

Necropsy.—There were: edema of the brain and leptomeninges; pseudomembranous colitis; hyperplasia of the thymus, the mesenteric lymph nodes and the solitary lymphoid follicles of the lining of the bowel; fatty changes of the liver, and cloudy swelling of the kidneys.

Examination of the Brain.—On macroscopic examination, the meninges were found to be smooth and transparent. The pial vessels were distended with blood. The gyri were generally flattened and the sulci somewhat obliterated.

On microscopic examination, the pia-arachnoid was found to be moderately thickened and contained a few cells, mostly mesothelial elements, together with cells of irregular shape. The blood vessels were engorged, the vessel walls moderately thickened. No perivascular infiltration was noted.

Parenchyma: The most striking changes were found in the cortex. The majority of the ganglion cells had undergone a process of liquefaction. In some sections, numerous fields in succession could be examined without encountering a single ganglion cell with a normally preserved cytoplasm. Various stages of the liquefying process could be traced. In some of the cells the cytoplasm contained vacuoles of various sizes giving the interior of the cell body and the processes a honeycombed appearance. At the periphery of the cell, it looked as

7. Stooss, Max: Acute Encephalitis im Kindesalter. Eine selbstaendige Infektionskrankheit, Schweiz. med. Wchnschr. **56**:758 (Aug. 7) 1926.

8. Grinker, R. R., and Stone, T. T.: Acute Toxic Encephalitis in Childhood, Arch. Neurol. & Psychiat. **20**:244 (Aug.) 1928.

9. Brain, W. R.; Hunter, D., and Turnbull, H. M.: Acute Meningo-Encephalomyelitis of Childhood, Lancet **116**:221 (Feb. 2) 1929.

10. Kemkes, B., and Saenger, S.: Ueber Encephalitis des Kindes, Monatschr. f. Kinderh. **32**:334 (June) 1926.

11. Marsh, N. P.: Four Cases of Acute Non-Suppurative Encephalitis in Children, Brit. J. Child. Dis. **7**:241 (June) 1910.

if a continuous series of spherical holes had been punched into the marginal area so that the outline appeared frayed and eaten away (fig. 1). The stainability of the cytoplasm was markedly reduced. In other cells, no honeycomb appearance was discernible, but the cytoplasm had undergone a process of massive liquefaction and showed corresponding defects. Two types of massive defects could be distinguished: (1) the cytoplasm was liquefied only around the nucleus and an empty perinuclear zone had formed between the nucleus and a peripheral strip of an ill staining cytoplasmic mass (fig. 2); (2) even the remnant of stainable

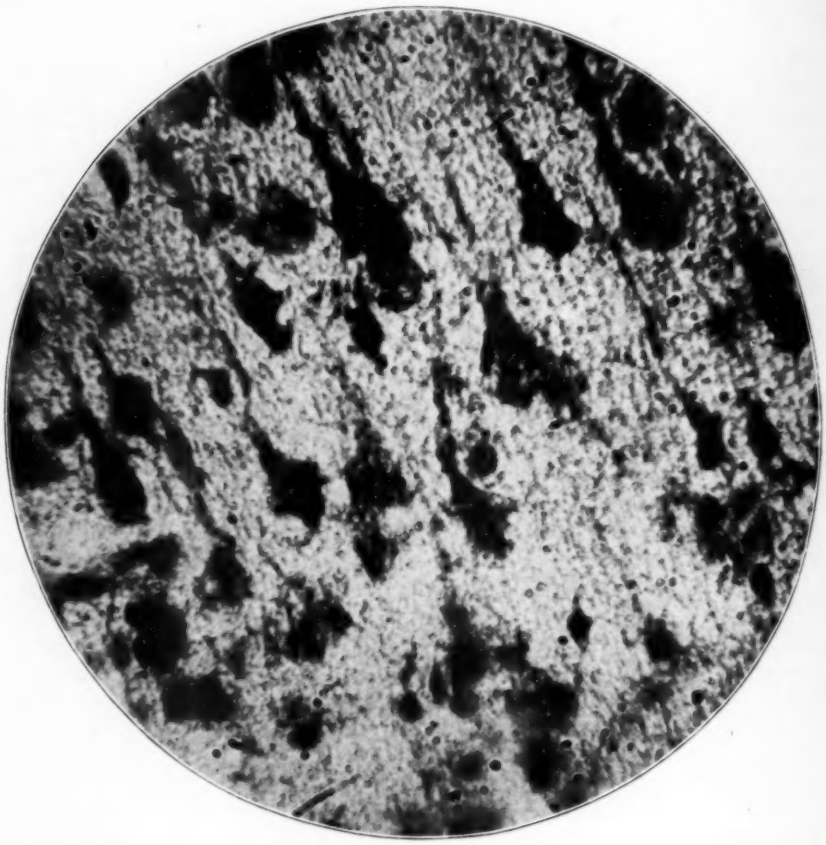

Fig. 1 (case 1).—Occipital region. The cytoplasm of the ganglion cells is vacuolated and frayed at the edges. The processes are swollen, vacuolated, tortuous and varicose. Toluidin blue; × 720.

substance had disappeared, leaving an isolated nucleus situated in the center of a cavity the borders of which recalled distinctly the outlines of a ganglion cell (fig. 3). In many of these massively liquefied ganglion cells one or two glia nuclei were found, either in the empty perinuclear space or in the peripheral strip of cytoplasm (fig. 2). Practically none of these ganglion cells showed dendrites. In most sections, the ganglion cells with massive liquefaction largely outnumbered those with vacuoles. When this was the case, e. g., in the parietal

and occipital lobes, the impression was gained that the number of ganglion cells per field was markedly diminished as compared with the fields in which the vacuolated cells predominated.

The nuclei of the ganglion cells exhibited characteristic changes. On the whole they manifested a much greater vitality than the cytoplasm, having managed to survive even when the cytoplasm was totally destroyed. However, they underwent profound modifications: Some nuclei were swollen and exhibited an irregularity of outline, but in most instances the outline was sharp, the form being triangular, oval or round, the triangular type predominating. A folding of the membrane was not observed. The nucleolus was, on the whole, easily visible and flanked by two or three paranucleoli. The stainability, though generally reduced, was distinctly in a better state of preservation than in the cytoplasm.

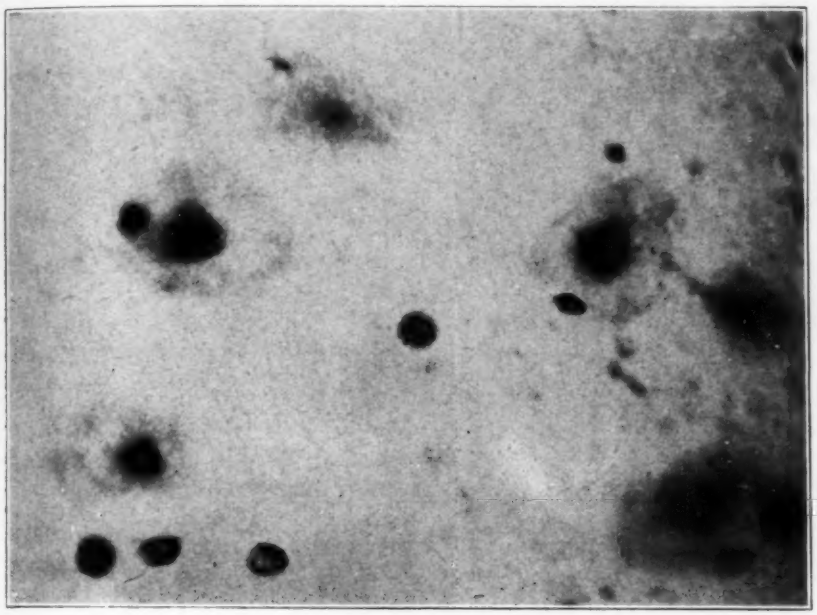

Fig. 2 (case 1).—Parietal region. The cytoplasm of the ganglion cells is liquefied within the perinuclear space. Peripheral strips of cytoplasmic substance are preserved. Note the glia nuclei within the ganglion cells. Toluidin blue; × 1100.

In spite of the relatively good state of preservation of outline, size and stainability, almost every nucleus showed some signs of regressive alteration. The milder changes were characterized by an accumulation of deeply stained granules along the periphery. The appearance then was of a more or less homogeneous mass, containing a centrally located nucleolus and bordered by a continuous string of deeply stained chromatin beads. At a further stage, the peripheral ring of granules had become more pale and dustlike and the nucleolus, equally pale, had moved toward the periphery. As a still further development, it was observed that the previously homogeneous mass in the interior of the nucleus had undergone granulation. Coincident with this granular transformation, both the nucleolus and the peripheral ring of well stained granules had disappeared. Two or

three paranucleoli could still be discerned. The last stage of nuclear disintegration was represented by a pale, dustlike mass which could be identified as the remnant of a nucleus only by its size and outline. Liquefaction and vacuole formation were not observed in the nucleus.

An equally intense degree of disintegration was noted in the cytoplasmic processes of the ganglion cells. They were enormously elongated and in some sections so prominent that they dominated the field. In the regions in which the

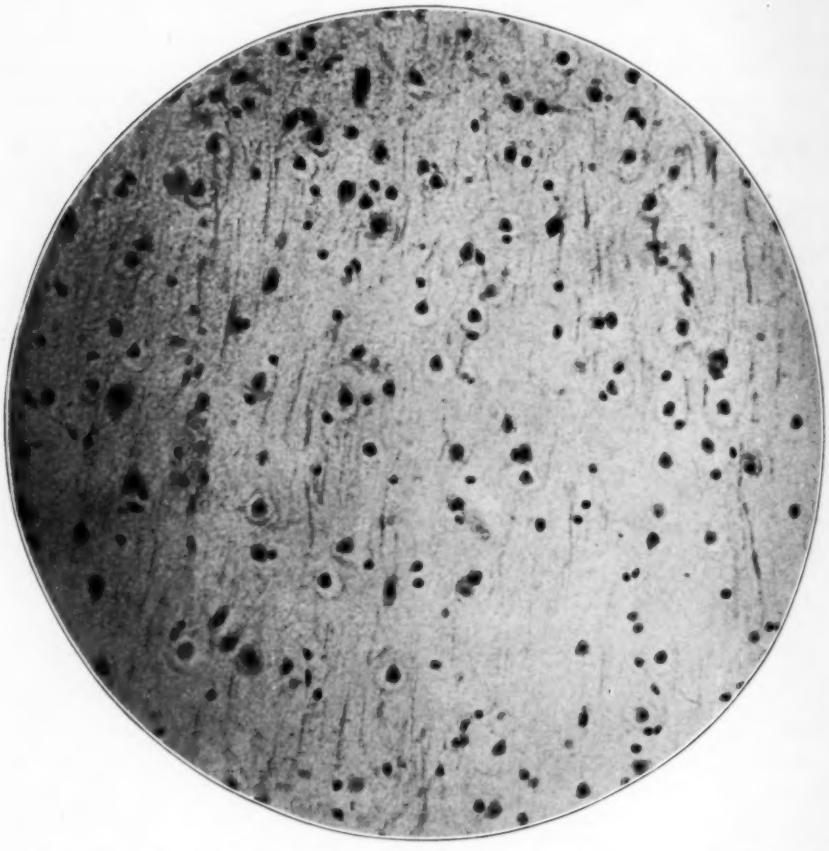

Fig. 3 (case 1).—Occipital lobe. In most of the ganglion cells the cytoplasm is completely liquefied. The nucleus is preserved. The thin, pale strands running between the cells are broken up dendrites. The ganglion cells appear reduced in numbers. Toluidin blue; × 320.

ganglion cells had reached an extreme degree of liquefaction and the isolated nuclei prevailed, there were seen only remnants of axons whose connections with the cell body could not be traced. In the better preserved areas the processes were still continuous with the cell body, somewhat thickened, tortuous and varicose, others thin and threadlike, either running in a straight line or winding in corkscrew fashion. Most of them were vacuolated. The vacuoles either formed narrow meshes in the cell processes, giving rise to a honeycomb appearance, or

were located mainly along the outer edges making the borders appear frayed and eaten away. Many of the processes appeared as long, drawn-out shadows. Axonophagia was seldom noted.

In the basal ganglia, the changes in the ganglion cells were considerable but less acute than those in the cortex. The small cells of both the corpus striatum and the thalamus were generally well preserved. The large ganglion cells, however, were greatly damaged, the main features being swelling and vacuolation of the cell body and of the processes. A massive liquefaction of the cytoplasm, with naked nuclei as a residuum, was not noted. Central and peripheral chromatolysis was very prominent, and neuronophagia and satellitosis were frequently observed.

In the cerebellum, the Purkinje cells exhibited acute changes. Some of them had a pyknotic, narrowed and elongated body, but the majority were swollen and—in sections with well stained granular cells—stained badly. The cell processes were swollen, tortuous and varicose, and expanded, antler-like, in all directions. Cell shadows were frequent. Progressive disintegration of the nucleus, as seen in the cortex, could be traced here in similar stages. The nucleolus and the paranucleoli were last to disappear. The granular and molecular layers showed no particular changes.

The glia of the cortex consisted mainly of oligodendroglia. In toluidin blue sections the nuclei stained deeply. Their chromatin substance was usually lumped together in thick granules which were massed in an eccentric ring along the periphery (peripheral hyperchromatosis). In other instances, the granules filled and densely crowded the entire cell body (generalized hyperchromatosis). Again, in other cases, the glia nucleus appeared expanded and the chromatin granules were pale, small and irregularly distributed over the cell body. Some of the nuclei had lost their sharp outline, and the chromatin substance was reduced to an irregular dustlike mass (karyolysis). A number of the glia nuclei were pyknotic. Mitotic figures were nowhere observed.

In the subcortex, the midbrain and the cerebellum, the majority of the glia cells had distinct cytoplasmic processes. As a rule, the cytoplasm did not surround the nucleus on all sides but accumulated at two poles only. The cell as a whole had a rhomboid shape, with the two homogeneous cytoplasmic processes tapering off streamer-like from the nucleus. Some cells possessed only one cytoplasmic process. The nucleus was deeply stained and exhibited in most instances a peripheral hyperchromatosis. Many of the glia cells showed a tendency to coalesce and to form so-called gliarasen. Other cells tended to mass along the course of the blood vessels. In longitudinal sections they appeared as dense accumulations on one side of the blood vessel. In cross-sections they appeared crowded at one pole. Karyorhectic and karyolytic phenomena were not observed. Pyknotic nuclei were much rarer than in the cortex. In the corpus striatum small areas with typical ameboid glia cells were seen (fig. 4). The nuclei were pyknotic, the cytoplasm homogeneous and expanding in all directions, frequently forming pseudopodia. Gliarasen and glia rosets were conspicuous in the basal ganglia.

In practically all sections, a well defined glia reticulum was present; especially when stained according to the method of Holzer, it was brought out with great distinctness as an irregular network, formed by strands of various thickness and enclosing vacuoles of various sizes (fig. 5). The larger vacuoles were usually found in the more damaged areas, especially in the cortex. In the subcortex, the basal ganglia, the pons and the cerebellum, the reticulum was generally characterized by small round meshes which were bounded by fine strands of thin fibers. In these small meshed areas the relationship between the glia nuclei and

the reticulum could not be determined, as several meshes were often covered by one glia cell. Where the meshes were large, the glia nuclei were situated at the nodal point at which the fibrils of the reticulum intersected. In regions with cytoplasmic glia, the cell processes were distinctly differentiated from the reticulum.

The arteries and the veins were generally distended and congested throughout the brain. In many arteries, the wall appeared thickened and contained numerous

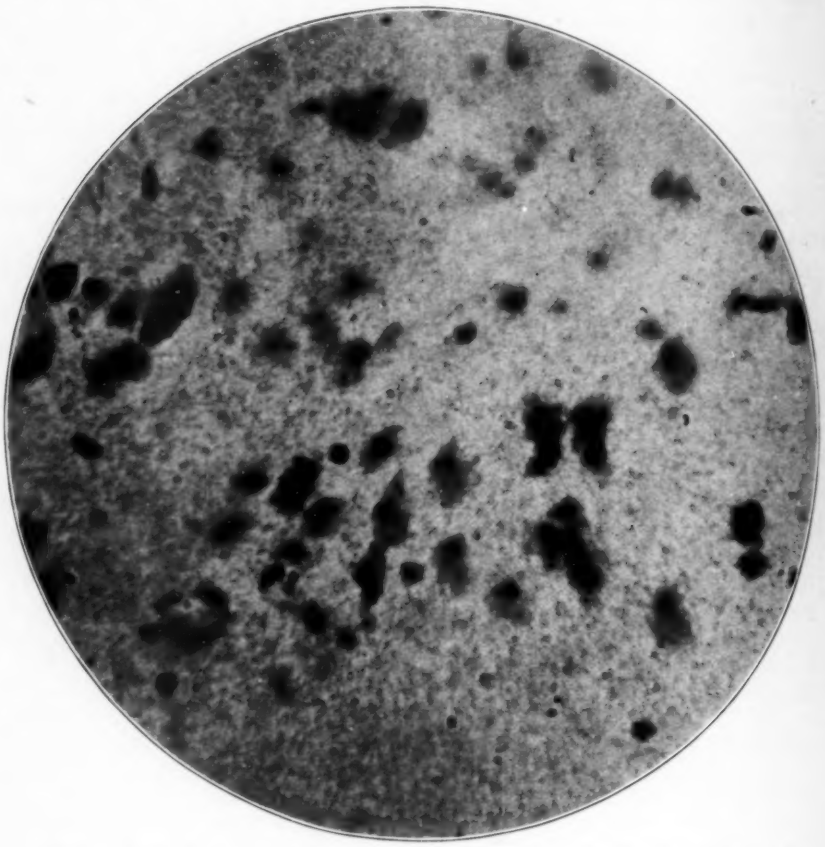

Fig. 4 (case 1).—Corpus striatum. Ameboid glia. Toluidin blue; × 800.

adventitial cells. Perivascular infiltration was seen nowhere. The capillaries were also distended and congested and their endothelial cells markedly swollen. Newly formed capillaries were numerous, especially in the regions outside the cortex. Their endothelial cells were usually swollen and protruding. Budding was occasionally seen. In the basal ganglia many blood vessels were filled with a colorless homogeneous mass which looked like coagulated serum, and large globules of the same mass were found in the widened spaces of His. Sometimes one part of the blood vessel was filled with the coagulated mass, while the other part contained blood corpuscles. Fibrin was absent from the coagulated substance. Only in the basal ganglia were these coagulations noted.

Summary.—A child with high fever, coma, convulsions, spasticity and a bilateral Babinski sign died two days after the onset of the symptoms. In spite of the short duration, the pathologic changes were intense, except in the meninges, in which only a mild increase in cells was found. The ganglion cells showed either marked vacuolation of the cell body and the cell processes or massive liquefaction. The nuclei of

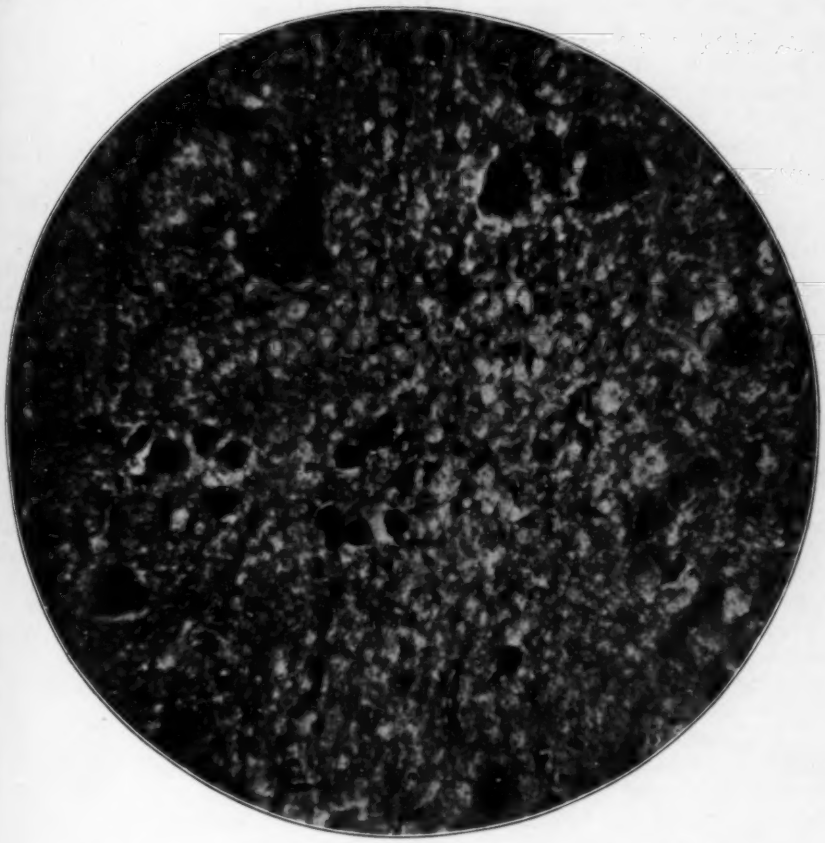

Fig. 5 (case 1).—Parietal area. Glia reticulum. Holzer; × 720.

the ganglion cells were usually preserved but underwent a progressive granular disintegration. The glia presented predominantly regressive changes in the cortex (hyperchromatosis and karyolysis) and predominantly progressive changes in the noncortical areas (cytoplasmic glia). Ameboid glia was found only in the corpus striatum. A well pronounced glia reticulum was present practically throughout the brain. The blood vessels showed, in the main, distention and congestion and, in the basal ganglia, coagulation of the serum. Newly formed capillaries

with swollen and protruding endothelial cells were found everywhere. They were more prominent, however, in the noncortical regions than in the cortex.

Case 2.—*History.*—A white, Polish girl, aged 5 years and 7 months, was admitted to the Children's Memorial Hospital on Feb. 2, 1924, and died twenty hours later. The girl had been well until three days before admission, when fever developed and she complained of headache. Twelve hours before admission, she became unconscious and very high fever developed.

Examination.—When seen at the hospital, the child was in deep coma and had a temperature of 103.8 F. The respirations were rather deep and rapid. The pupils were dilated, the right being larger than the left, and reacted fairly well to light. The vessels of both optic disks were engorged. No other cranial nerve changes were demonstrable. A slight rigidity of the neck and some rigidity of the extremities, especially of the right side, were noted. A bilateral Babinski sign was present. There was no ankle clonus. The patient had no convulsions. The pharynx was swollen and red. The chest was normal; the heart sounds were not clear. The heart rate was from 150 to 160. Many petechial hemorrhages were present on the skin of the trunk and the extremities. Physical examination otherwise gave normal results. The white blood count was 21,200 with 70 per cent polymorphonuclears and 30 per cent lymphocytes. There were 540 cells per cubic millimeter in the spinal fluid, of which 65 per cent were polymorphonuclears and 35 per cent lymphocytes. Tests for globulin were strongly positive. The temperature remained high, reaching 106 F. before death. Except for an increased rigidity of the extremities, the neurologic observations did not change.

Necropsy.—There were: recent vegetative and ulcerative mitral endocarditis; slight hypertrophy of the heart; multiple mycotic emboli in the kidneys, liver, skin and lining of the bowel; abscesses of the kidneys and liver; acute edema and hyperemia of the brain; foramen magnum pressure furrow of the base of the cerebellum; unequal pupils; acute hyperplasia of the spleen; hemorrhage into the mesenteric and peri-aortic lymph nodes; acute emphysema of the lungs; petechial hemorrhages into the pleurae and lining of the stomach and bowel; slight serous peritonitis and right pleuritis; cloudy swelling of the kidneys and myocardium; passive hyperemia of the lungs, liver and kidneys; hyperemia of the lining of the trachea, and fatty changes of the liver.

Examination of the Brain.—On macroscopic examination the meninges were found to be smooth and transparent. The convolutions were flattened, the sulci largely obliterated. A foramen magnum pressure furrow was noted on the dorsal surface of the cerebellum. The cut surfaces showed no gross pathologic changes.

On microscopic examination, the pia-arachnoid and its prolongations showed moderate thickening and were rich in cells, especially over the occipital region. The cells consisted chiefly of mesothelial elements and fibroblasts. A few lymphocytes and polyblasts were also seen. The meningeal blood vessels were distended and congested. Some of them were filled with a coagulated homogeneous mass.

Parenchyma: In the central and occipital areas the ganglion cells showed extensive, both total and perinuclear, massive liquefaction. Many of the liquefied empty spaces contained glia nuclei. Denuded ganglion cell nuclei were numerous in these regions. These nuclei showed the same stages of gradual disintegration as in case 1. Outside the central and occipital areas, a massive liquefaction was only occasionally observed. Most of the ganglion cells here were swollen and

vacuolated and had elongated, swollen and tortuous processes. The nuclei of the vacuolated cells were often displaced toward the periphery, but granular disintegration was not frequent. The vacuolated cells showed some evidence of neuronophagia and axonophagia. In the basal ganglia, the majority of the large ganglion cells were chromatolyzed but little vacuolated. Neuronophagia and satellitosis were conspicuous. The nucleus was usually misplaced and the membrane folded. The small ganglion cells appeared little damaged. The Purkinje cells of the cerebellum were, in most instances, enormously swollen; their processes were thickened and vacuolated and radiated in all directions.

The cortical glia consisted mostly of oligodendroglia. Most of the glia nuclei showed peripheral or general hyperchromatosis. Swollen oligodendroglia was occasionally seen. In the subcortex and in the basal ganglia, numerous cytoplasmic glia cells were present, side by side with oligodendroglia. The latter was often arranged in one or two rows alongside the blood vessels. Gliarasen and glia rosets were often seen. The glia reticulum was pronounced in the entire cortex, in part of the subcortex and in the cerebellum. In the basal ganglia and in the pontomedullary region, it was little developed.

The blood vessels were generally distended and congested throughout the brain. Plasma cells were seen in the lumens of most blood vessels, but none was noted outside the vascular sheaths. Newly formed capillaries were present everywhere, but in the noncortical areas they were more numerous than in the cortex. Leukocytic thrombi were occasionally seen.

Summary.—A child, aged 5 years and 7 months, developed high fever, coma, pupillary changes, rigidity of the extremities and a bilateral Babinski sign and died after three days. The brain showed microscopically a condition which, in many points resembled that in case 1. The meninges were generally thickened and richer in cells. The ganglion cells of the cortex were either vacuolated or massively liquefied, the liquefaction not being as extensive as in the former case. The glia changes were practically identical in both cases, except that in case 2 ameboid glia was not present, and the glia reticulum was missed in some areas in the noncortical regions. Particular features of case 2 were the plasma cells, seen in the lumens of most blood vessels, with no plasma cell infiltration of the vessel walls or of the perivascular spaces. Formation of new capillaries and distention and congestion of the blood vessels were as prominent as in case 1.

Case 3.—A boy, aged 5 weeks, admitted to the Children's Memorial Hospital on Aug. 12, 1925, had been apparently well until a few days before admission, when he became irritable and drowsy. Three days before admission, generalized clonic and tonic convulsions occurred several times during the day. Two days before admission, a moderate jaundice developed. Further details of the illness could not be obtained. The child was born by normal delivery and weighed 1980 Gm. Breast milk had been given during the first two weeks, afterward a commercial brand of condensed milk.

Examination and Course.—On admission, a physical examination revealed a moderately jaundiced, spastic baby. The fontanel admitted three fingers and was not bulging. The pharynx was moderately red and swollen, and a mucopurulent discharge came from the nose. The chest and abdomen were normal, except

that the liver was palpable two fingers breadths below the costal margin. The sensorium was not clear. The pupils were equal and reacted to light. There was no rigidity of the neck. The legs were flexed and rigid. The hands were clenched. The temperature was 102 F. and ranged between 102 and 104 during the course of the illness. The spinal fluid was clear and contained 18 cells per cubic millimeter. The globulin tests were positive. The Wassermann reaction was negative. The sugar content was 58 mg. The white blood count was 12,600, with 61 per cent polymorphonuclears and 39 per cent lymphocytes. The red blood count was 900,000. The hemoglobin was 70 per cent. The urine was normal.

On the second day after admission, the patient had clonic convulsions, more severe on the right side than on the left, which continued in spite of the administration of chloral and bromides. During the following ten days, the general condition of the patient did not change. There were many convulsions each day, especially marked on the right side. The patient was semicomatose. The spinal fluid, obtained on the tenth day in the hospital, showed a cell count of 202 per cubic millimeter and strongly positive globulin tests. The sugar content was 60 mg. The patient died in convulsions on that day.

Necropsy.—There were: edema of the brain and of the leptomeninges; distended urinary bladder; cholangitis; generalized icterus; slight bronchopneumonia of the right upper lobe; cloudy swelling of the kidneys and myocardium; passive hyperemia of the liver; moderate emaciation, and hyperplasia of the mesenteric lymph nodes.

Examination of the Brain.—On macroscopic examination, the pia-arachnoid was found to be smooth and transparent except over the interpeduncular space where it appeared opaque and thickened. The gyri were narrow and markedly flattened and the sulci partly obliterated. On the cut surfaces nothing of note was observed.

On microscopic examination, the meninges were generally thickened and cellular, especially over the pons and the occipital lobe (fig. 6). Most of the cells were mesothelial cells and fibroblasts. Macrophages, polyblasts and lymphocytes were also seen occasionally. The blood vessels were moderately distended and congested and their walls appeared thickened. Perivascular infiltration was not present. The pial prolongations between the cerebral convolutions showed a particularly strong cellular and vascular reaction.

Parenchyma: The ganglion cells of the cortex showed, in the main, the two types described in the foregoing cases. The cells with massive liquefaction, however, were found in considerable numbers in the motor area only. In other areas, the cells with vacuole formation and with the fraying of the cell borders were the outstanding features. Some neuronophagia and axonophagia were present. Granular disintegration of the nucleus was less frequently observed than in the preceding two cases. The cells with massive liquefaction had lost their processes altogether, while in the cells with vacuole formation the processes were swollen, vacuolated, tortuous and varicose. The borders of the cell processes had the appearance of being eaten away. Nowhere outside the cortex were cells with massive liquefaction. In the basal ganglia the vacuolation was most marked, in both the large and the small ganglion cells. Neuronophagia and axonophagia were rather conspicuous. In the pons, the vacuolation was insignificant and the changes limited to a moderate process of chromatolysis and to some neuronophagia. In the cerebellum, both granular and Purkinje cells were practically unaffected.

The cortical glia consisted, for the most part, of oligodendroglia, with peripheral and general hyperchromatosis as a prominent feature. Some of the glia

nuclei were pyknotic. Ameboid glia was not seen. In the subcortex, the basal ganglia and the pons, cytoplasmic glia predominated. As in case 1, the cytoplasm was often arranged in a bipolar fashion. Gliarasen and glia rosets were frequent. Extravascular glia accumulation in one or two rows was much in evidence. The glia reticulum was well developed throughout the brain.

The blood vessels were generally distended and engorged. The walls appeared thickened and showed a proliferation of the endothelial and, more especially, of the adventitial elements. No perivascular infiltration was noted. Newly formed

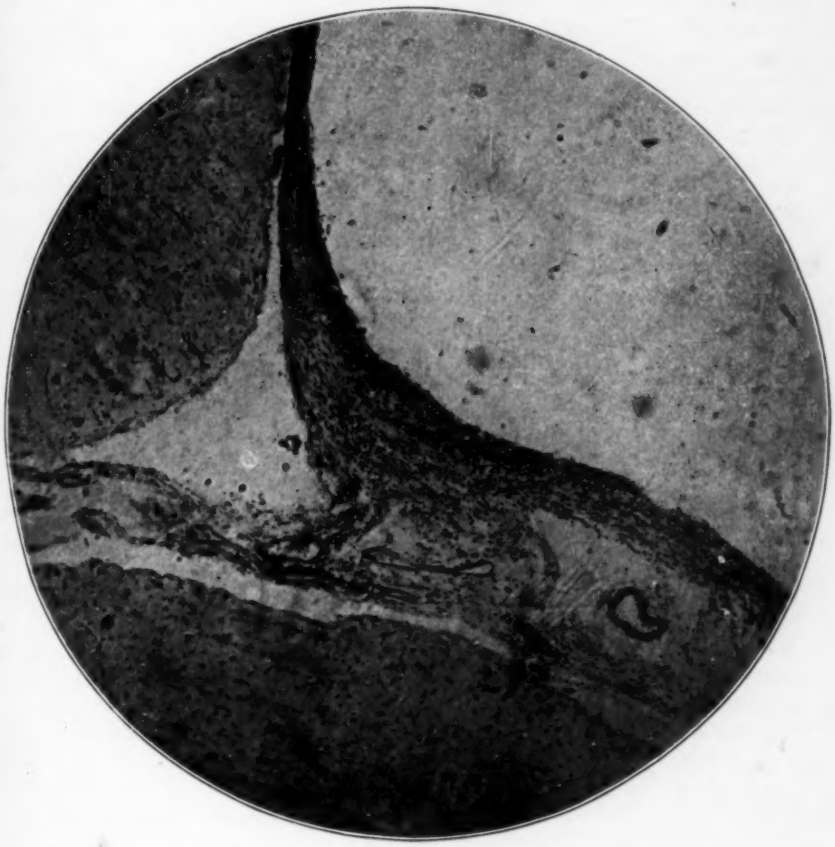

Fig. 6 (case 2).—Occipital lobe. The meninges and the subarachnoid space are thickened and cellular. Toluidin blue; × 160.

capillaries were more frequent in the noncortical regions than in the cortex. The endothelial cells of the capillaries were swollen, deeply stained and protruding. Plasma cells were not found.

Summary.—A boy, aged 5 weeks, developed high fever, convulsions, drowsiness and spasticity of the extremities and died within thirteen days. The microscopic changes of the brain coincided in many details

with those in the first two cases. However, there were some marked differences. The massive liquefaction of the cortical ganglion cells, which in case 1 dominated most of the fields and in case 2 was still much in evidence, was here pronounced only in the motor region. The predominating features were the cells with vacuole formation. The glial and vascular changes were essentially the same as in the other cases, except that the ameboid glia, found in case 1, and the plasma cells, seen in case 2, were here absent. The glia reticulum was well developed. The meningeal reaction was stronger than in both preceding cases.

Case 4.—*History.*—A white boy, aged 4 months, admitted to the Children's Memorial Hospital on Oct. 17, 1924, had been well, except for a slight cough of several days' duration, until two days before admission, when he began vomiting and having from five to ten yellow-green watery stools per day. The birth had been normal without instruments. There were no cyanosis, fever, jaundice or convulsions. A commercial brand of condensed milk was given from birth. No vomiting or diarrhea preceded the onset of the illness.

Examination and Course.—The child was restless, irritable, undernourished and undersized, and acutely ill, with deep, pauseless respirations, a slight flush to the cheeks, and a loud, shrill cry. The temperature was 100 F. The tissue turgor was fair. A slight rigidity of the neck and spasticity of the extremities were present. The fontanel was not bulging. The pupils were equal and reacted well to light. The eyes were fixed and staring. Except for a red, swollen pharynx and an occasional râle in the chest, the respiratory tract was normal. The reflexes were very brisk but equal on the two sides. A bilateral Babinski sign was present. The white blood count was 41,000, with 75 per cent polymorphonuclears and 25 per cent lymphocytes. The hemoglobin was 90 per cent. Except for a moderate amount of albumin, the urine was normal throughout. A lumbar puncture on the day of admission revealed a clear fluid, 6 cells per cubic millimeter and a sugar content of 105 mg.

During the first two days in the hospital the general condition improved. Feedings were retained, the diarrhea decreased, and the symptoms of intoxication disappeared. On the third day, however, the temperature, which had averaged 102, rose to 104 F. Symptoms of bronchopneumonia appeared, and marked neurologic signs developed. Extreme and rapidly changing eye observations were noted. The pupils at times were very unequal, with first one larger than the other; a few minutes later the reverse was true. External and internal strabismus alternated rapidly. There was marked rigidity of the extremities and slight rigidity of the neck. Fever of 103 F., Cheyne-Stokes breathing, marked rigidity of the whole body and a bulging fontanel were present on the fifth day in the hospital. A spinal puncture revealed a cell count of 35, a positive globulin test and 97 mg. of sugar. The patient died on that day, Oct. 25, 1924.

Necropsy.—There were: dissemniated bronchopneumonia; cloudy swelling of the myocardium and kidneys; marked fatty changes of the liver; hyperemia of the brain; edema of the leptomeninges; bilateral mucopurulent otitis media; Meckel's diverticulum.

Examination of the Brain.—On macroscopic examination, the pia-arachnoid was found to be generally smooth and transparent. The blood vessels were prominent and bulging. The convolutions were slightly flattened and somewhat obliterated. The cut surfaces showed normal conditions.

On microscopic examination, the meninges were thickened and cellular, especially over the cerebellum. There, numerous mesothelial cells, macrophages and fibroblasts were seen, together with occasional lymphocytes and polyblasts. The blood vessels were distended and engorged, their walls appeared moderately thickened. No perivascular infiltration was present.

Parenchyma: The ganglion cells of the cortex were, to a considerable degree, vacuolated, but their cell borders were not frayed. In some places the axons and dendrites were visible, slightly swollen and elongated. As a rule, however, they were either not visible at all or showed normal proportions. The nucleus was often displaced toward the periphery but mostly well preserved. Neuronophagia and satellitosis were prominent. Cell shadows were frequent. In the basal ganglia, vacuolation of the ganglion cells, especially of the large ones, was pronounced. Neuronophagia and satellitosis were here much in evidence. In the pons and the medulla the damage to the ganglion cells was insignificant. The Purkinje cells of the cerebellum were swollen and showed a moderate degree of chromatolysis. Their nucleus was usually well preserved.

The cortical and subcortical glia consisted mostly of swollen oligodendroglia. Hyperchromatosis, karyorhexis and fragmentation were very little in evidence. Ameboid glia cells, though not numerous, were present in most sections. In the basal ganglia and in the pontomedullary region, swollen oligodendroglia was prominent, but ameboid glia was absent. The glia reticulum was especially well developed in the cortex and subcortex. There, practically the whole extent of the substance was involved. In other parts of the brain many areas were found where no reticulum was visible. On transition from a region with reticulum to a region without reticulum, no marked difference in the intensity of the vascular or cellular changes could be seen.

The blood vessels were distended and congested throughout the brain. Their walls appeared often thickened, with a marked proliferation of the adventitial cells. Newly formed capillaries with hypertrophic endothelial cells were frequent, especially in the basal ganglia. Perivascular infiltration was absent and plasma cells were seen nowhere.

Summary.—A boy, aged 4 months developed vomiting, fever, diarrhea, transient pupillary changes and ocular paresis, rigidity of the neck and extremities, and a bilateral Babinski sign; he died after ten days. The brain changes were: localized thickening of the meninges, especially over the cerebellum, with numerous mesothelial cells, fibroblasts and macrophages; vacuolation of the ganglion cells of the cortex and basal ganglia, with swelling, vacuolation and elongation of their dendrites. Neuronophagia, satellitosis and the formation of cell shadows were conspicuous features. Swollen oligodendroglia was prominent, and the glia reticulum was well developed in the cortex and subcortex. Ameboid glia was present in almost all sections. The blood vessels showed distention and engorgement, and formation of new capillaries with swollen endothelial cells. No plasma cells were found.

CASE 5.—*History.*—A white girl, aged 3 years and 10 months, was admitted to the Children's Memorial Hospital on Jan. 3, 1925. The patient had apparently been well until eight days before admission to the hospital, when she became irritable and was thought to have a cold. Three days later, she had a fever of

104 F. and was very ill. The following day, the head was drawn back, the arms tightly flexed and the knees drawn up. During the two days prior to admission, she had had no fever but there was stiffness of the neck. Except for a convulsion a year before, the cause of which was not known, the previous history was without significance.

Examination and Course.—On admission to the hospital, the patient appeared acutely ill. The temperature was 102 F. She seemed rather dull and moaned constantly. The pharynx was red and swollen, the left ear drum red and bulging. The chest and abdomen were normal. The pupils were equal and reacted to light. There were jerking movements of the eyes that simulated nystagmus. Both fundi were normal. There was a bilateral Babinski sign and some rigidity of the extremities. The neck was somewhat rigid. The urine was normal. The white blood count was 7,000, with 49 per cent polymorphonuclears and 51 per cent lymphocytes. The red blood count was 5,180,000. The hemoglobin was 90 per cent. A spinal puncture revealed a clear fluid under increased pressure, a cell count of 8, negative globulin and 85 mg. of sugar. The Wassermann and Pirquet tests were negative.

During the first seven days in the hospital, the condition remained unchanged. On the eighth day, the patient developed a moderate attack of measles and double otitis media, with a purulent discharge from both ears. Some weakness of the neck muscles was present throughout the illness. There was rigidity of the right leg, with bilateral Babinski and Oppenheim signs and an exaggeration of all the deep reflexes. The cranial nerves were normal. There was rigidity of the neck, and the bladder was distended. A few days later, the patient developed bronchopneumonia and died.

Necropsy.—There were: huge serosanguino-fibrino-purulent pleuritis on both sides; compressed left lung; extensive bronchopneumonia of the left upper lobe; multiple abscesses of the upper lobe of the left lung; marked hyperemia of the endocardium; petechial hemorrhages into the pleura of the left lower lobe; cloudy swelling of the myocardium and kidneys; hyperplasia and hyperemia of the mesenteric and periaortic lymph nodes; bilateral sanguinopurulent otitis media; fatty changes of the liver; hyperplasia of the peribronchial and peritracheal lymph nodes; hyperemia of the lining of the trachea.

Examination of the Brain.—On macroscopic examination the meninges appeared smooth and transparent. The pial blood vessels were very prominent. Over the dorsal aspect of the cerebellum, a foramen magnum pressure furrow was present. The convolutions of the brain were flattened and the sulci partly obliterated. The cut surfaces appeared normal.

On microscopic examination, the pia-arachnoid was generally thickened and cellular. The cells were mostly fibroblasts and mesothelial cells. Macrophages, loaded with blood pigment, were also present. The blood vessels were enormously distended and engorged. Their walls appeared slightly thickened. Perivascular infiltration was absent.

Parenchyma: The changes in the cortical ganglion cells varied from a swelling of the cell bodies and their processes to central and peripheral chromatolysis and formation of cell shadows. Minute vacuoles, though not a prominent feature, were frequently observed. Neuronophagia and satellitosis were mild. In some places tumefaction and elongation of the dendrites were present. In the basal ganglia and the pons, the ganglion cell changes were, in the main, analogous to those of the cortex. The Purkinje cells of the cerebellum showed either swelling or pyknotic changes and various degrees of chromatolysis.

The majority of the glia cells had a well defined chromatin reticulum and a few chromatin granules. Hyperchromatosis and karyorhexis were infrequent. Cystoplasmic glia, glia rosets and gliarasen were especially common outside the cortex. The glia reticulum was fairly represented throughout the brain.

The arteries and veins were moderately distended and engorged. Newly formed capillaries with swollen endothelial cells were numerous. Plasma cells were found in most blood vessels, but within the lumen only.

Summary.—A girl, aged 3 years and 10 months, developed high fever, rigidity of the extremities, a bilateral Babinski sign, a bilateral purulent otitis media, and died after thirty-nine days from bronchopneumonia. The brain changes were as follows: The meninges were thickened, vascular and rich in fibroblasts, mesothelial cells and macrophages. The ganglion cells, especially of the cortex, showed swelling and vacuolation of the cell bodies and their processes; in addition, neuronophagia and chromatolysis. Cytoplasmic glia, gliarasen and glia rosets were particularly prominent outside the cortex. The glia reticulum was generally well developed. The blood vessels were distended and engorged, and new capillaries were numerous. Plasma cells were found in the lumen of most blood vessels.

COMMENT

The five cases studied in this series had several features in common, both positive and negative. The common negative features were: the absence of mesodermal elements in the perivascular spaces and the absence of hemorrhagic foci. The common positive features were: extensive damage to the cortical ganglion cells, progressive glial and active vascular reaction in the noncortical areas, the presence of a pronounced glial reticulum and a generally moderate meningeal reaction. All other features varied in the individual cases. The common negative features proved that the condition was neither inflammatory nor hemorrhagic. Since no evidence pointing to a purulent or parasitic infection could be found, the only etiologic alternative was the assumption of a toxic condition.

It is generally known that the changes in a toxic condition depend on the severity of the intoxication rather than on the specific type of the virus. This point was brought out convincingly by the experimental work of Lotmar [12] and Rosental.[13] These workers subjected large series of rabbits to the action of dysentery toxin and guanidin respectively, and obtained, with different toxins, practically identical

12. Lotmar, F.: Beitraege zur Histologie der acuten Myelitis und Encephalitis, sowie verwandter Prozesse, in Nissl and Alzheimer: Histologische und histopathologische Arbeiten ueber die Grosshirnrinde, 1913, vol. 6, p. 245.

13. Rosental, Stefan: Experimentelle Studien ueber die amoeboide Umwandlung der Neuroglia, in Nissl and Alzheimer: Histologische und Histopathologische Arbeiten ueber die Grosshirnrinde, 1913, vol. 6, p. 89.

changes. The changes bore a striking resemblance to those seen in the first three cases of this study. Hassin [14] was able to describe analogous conditions in the spinal cord in five cases of myelitis. Like Lotmar and Rosental, he concluded that, according to the intensity of the toxic agent, two conditions must be differentiated: type I, characterized by a peracute process of liquefaction with predominantly regressive glial changes, especially in the form of ameboid glia, and type II, characterized by an acute process of liquefaction, with predominantly progressive glial changes. While Hassin was mainly concerned with studying the glial changes, Lotmar and Rosental in their experimental studies also emphasized the ganglion cell changes. What Lotmar described as peracute liquefaction with regressive glial reaction (type I) constitutes a condition in which the ganglion cells become vacuolated and gradually disintegrate. The cell processes swell, become elongated, varicose and tortuous and are finally torn off. These ganglion cell changes are accompanied by an ameboid transformation of the glia. Lotmar and Hassin refer to this regressive character of the glia as a glial "insufficiency." In Lotmar's type II, the ganglion cell changes are essentially the same as in type I. But the glia proliferates and proves "sufficient" to aid in the repair. Hassin and Rosental emphasized that, in human beings, the two conditions overlap.

The foregoing classification can be applied, with the modifications necessary for human pathology, to the cases here recorded. In case 1, an extensive liquefaction was present which terminated in death after two days. The condition was a peracute liquefaction with disintegration of the ganglion cells. The glial changes were distinctly regressive in the cortex. But ameboid glia was found only in the corpus striatum. Case 1, therefore, may be said to correspond with Lotmar's type I. Cases 2 and 3 were also characterized by extensive liquefaction. But as the duration of the disease was four and thirteen days respectively and as the glial changes were less severe, they corresponded rather with Lotmar's type II. In cases 4 and 5 the liquefaction was comparatively insignificant and the regressive glial changes—moderate ameboid glial formation in case 4—were overshadowed by the progressive glial proliferation. The toxin had here obviously caused little damage to the ganglion cells and had left the glial elements in a state of "sufficiency." These cases can also be identified with Lotmar's type II. The toxic effect was here of a mild nature and the condition theoretically accessible to repair.

In case 1 the nuclei of the ganglion cells had undergone granular disintegration. In cases 2 and 3 this disintegration was present but less

14. Hassin, G. B.: Histopathological Changes in Five Cases of Myelitis, M. Rec. **90**:619 (Oct. 7) 1916.

noticeable, and in cases 4 and 5 it was practically absent. It would appear that the peracuteness and acuteness of the process are largely dependent on this nuclear disintegration. As long as the nucleus remains intact, the cell has still retained much of its vitality.

What the foregoing investigators term acute and peracute liquefaction is identical with what, in this paper, is called vacuolation. The ganglion cells in cases 1, 2 and 3 however presented a condition which could not be identified with this process of vacuolation. Many of these ganglion cells—in case 1 their majority—showed massive defects in their cytoplasm, either perinuclear or total, with a corresponding partial or total denudation of the nucleus. No description of this condition could be found in the available literature. The possibility of a postmortem change had to be considered. Spielmeyer [15] stressed the frequency of postmortem changes in infant brains. But various reasons argued against the assumption of an artefact. The main reason was the presence of glial nuclei in many of these massively liquefied ganglion cells. In addition, if the massive liquefaction occurred post mortem, it would be difficult to explain why the nucleus was almost always preserved and why the liquefaction was confined to the ganglion cells of the cortex only. According to Pfeifer,[16] the cortex has a well defined angio-architecture, analogous to its cyto-architecture, and selective regional changes could easily be explained on this basis. That post mortem changes should follow such a regional selection is hardly to be assumed.

In all five cases a pronounced glial reticulum was found. Under normal conditions, this reticulum is seen only in the subpial layer of the cortex. Its occurrence in other parts of the brain must be considered as pathologic. What Brown and Symmers [6] described as "vacuolation of the ground substance" is evidently identical with this reticulum. Held,[17 18] who first described the glial reticulum, maintained that it forms a continuum with the glia and that it has both a supporting and a nutritional function. Alzheimer [19] was rather skeptical about the

15. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p. 73.

16. Pfeifer, R. H.: Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928.

17. Held, Hans: Ueber die Neuroglia marginalis der menschlichen Grosshirnrinde, Monatschr. f. Psychiat. u. Neurol. **26**:360, 1909.

18. Held, Hans: Ueber den Bau der Neuroglia und ueber die Wand der Lymphgefaesse, in Haut und Schleimhaut: Abhandl. d. mathem-physikal. Klasse der koenigl. saechs. Ges. d. Wissensch. **48**:201, 1904.

19. Alzheimer, Alois: Beitrage zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgaengen im Nervengewebe, in Nissl and Alzheimer: Histologische und histopathologische Arbeiten ueber die Grosshirnrinde, 1909-1910, vol. 3, p. 401.

continuity of the reticulum with the glia and doubted whether the majority of the glial cells have "completely lost their individuality in favor of this network." As to its nutritional and supporting function, there seems to be general agreement. In the present series, the reticulum was practically of the same extent in all five cases. It appears to be a safe conclusion that it presented the basic and primarily fatal disturbance. This was evidenced by the observations in cases 4 and 5. In them the ganglion cell destruction had not advanced far, and the glial and vascular changes were in the direction of activity and progressiveness. The conditions were thus favorable to a restitution. That the restitution failed to take place may be ascribed to the disintegration of the reticular substance.

CONCLUSIONS

1. Two types of toxic encephalitis in children may be distinguished, one with peracute liquefaction and predominantly regressive glial changes, especially in the cortex, and another with acute liquefaction and predominantly progressive glial changes.

2. The peracuteness or acuteness of the process depends largely on the virulence of the toxin.

3. The ectodermal elements are primarily and preeminently affected.

4. The formation of a glial reticulum is the most important glial change.

5. Perivascular infiltration, as seen in infectious types of encephalitis, is absent.

6. The mesodermal reaction may show as a hypertrophy of the endothelial cells and as a hyperplasia of the adventitial cells.

STUDIES ON THE PATHOGENESIS OF MULTIPLE SCLEROSIS *

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Information about the pathology of multiple sclerosis is fairly complete so far as it concerns the lesions in the central nervous system. Two main principles stand out: destruction and removal of the myelin from around the axis cylinder, and gliosis. While there has been dispute as to whether the myelinolysis or the gliosis is primary, it is now generally believed that the myelinolysis comes first. Nothing is known of the causes of the myelin disintegration and most of the contemporary interest revolves around its being either purely degenerative on the one hand, or the result of inflammation on the other. There have been no definitely successful attempts to learn whether the disease can be transmitted by inoculations with any of the body fluids from patients, such as blood and spinal fluid.

The aim of the present investigation was to determine whether the blood of patients with multiple sclerosis contains any element that will cause myelin to disintegrate. Studies of animals into which such blood has been injected are infinitely complicated and have yielded little of promise. It was thought that a more direct means of testing the question would be to place blood in immediate contact with myelin. Myelin is best procured for such a purpose in parts of the central nervous system removed from freshly killed animals.

Pieces of spinal cord—in this case from rats—were immersed in blood from patients with multiple sclerosis. As will be seen, the difficulties in procuring fresh cords from human beings at the proper moments have obviated their use for the present.

This report deals with the results of experiments in which only oxalated blood plasma was utilized. That step alone is completed. The results obtained seem to point in a definite direction. If they are correct, it would seem that the oxalated blood plasma of these patients contains something that will cause myelin to disintegrate.

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TECHNIC

All experiments were performed under sterile conditions. Most of the fluids were subsequently cultured, and the few that were contaminated were discarded.

In each experiment, blood was drawn from a patient with multiple sclerosis as well as from a supposedly normal person, usually a medical student. A few of the blood specimens were drawn, and the whole experiment performed, under oil. That this procedure is futile, however, is evident from the facts that the experiment lasts for more than twenty hours and that much diffusion of carbon dioxide takes place through the oil. As would be expected, the experiments with oil gave the same results as the others. Clotting was prevented by the addition of a measured amount of sodium oxalate (10 mg. of the powder to each 5 cc. of blood). After centrifugation, 5 cc. of each plasma was placed in a separate sterile Stender dish. A rat was immediately killed with ether; the spinal cord was removed and cut into segments from the midcervical to the midlumbar regions. Pieces were immersed in the plasma and the dishes were covered, sealed with sterile petrolatum and placed in an incubator, where they remained at 37 C., usually for twenty-four, but sometimes for thirty-six or forty-eight hours. In every case the same rat spinal cord was used with both specimens of blood. The segments of the cord were then fixed in formaldehyde and stained with hematoxylin and eosin or by the Marchi or Weigert-Pal methods. In a few instances, at the suggestion of Dr. Cornwall, the cord was fixed in formaldehyde for from eighteen to twenty-four hours prior to the experiment. The final result was determined by comparing sections of the spinal cord immersed in plasma from normal persons with those immersed in plasma from patients with multiple sclerosis. The sections used were always from the center of the specimen. A segment from the upper cervical region of each spinal cord was fixed in formaldehyde immediately after removal from the rat, and was later stained as a control.

There were seventeen patients in all, on whom forty-two experiments were performed. Some patients were utilized two and three times; in some, various periods of incubation were tried, while in others both fresh and formaldehyzed rat cords were used.

Details of Technic.—1. Drawing the Blood: The blood is drawn into an ordinary 30 cc. syringe. The piston of the syringe is usually covered with sterile petrolatum to make it air-tight. The normal and diseased subjects are together, and as soon as the bleeding of one is finished, work is started on the other. The patient has been utilized first in some instances and the normal subject in others.

2. Immediate Disposition of the Blood: The blood is immediately placed in centrifuge tubes containing 10 mg. of sodium oxalate powder for each 5 cc. of blood to be used and is gently shaken. The amount of blood obtained was always approximately the same, so it can be said that, within the limits of unavoidable error—and these are small limits—the ratio of oxalate to blood was always the same. In some experiments these tubes contained liquid petrolatum; the final results were the same whether or not the blood was under oil. The blood specimens are centrifugated together for half an hour at a speed of from 800 to 1,400 revolutions per minute. Five cubic centimeters of each plasma is pipetted off and placed in sterile Stender dishes.

3. Preparation of the Spinal Cords: The plasma is left standing while the rats are killed and the spinal cords made ready. This interval is of varying duration, but checking of the results shows that no difference is made by it. The rats are placed in a bell jar with ether, where they remain until dead. The cords are rapidly dissected out and cut into pieces about 3/8 inch (0.9 cm.) long from the midcervical to the midlumbar region. Fine scissors are used for this

purpose. The uppermost piece is placed directly in 10 per cent commercial formaldehyde. Two others are immersed in the plasmas—one in each dish. The remaining ones are used for other experiments, which will be described subsequently. The order of cord segments is varied in alternate experiments. In one experiment the second piece down goes into the diseased plasma and the third into the normal plasma; this is reversed in the next set.

4. Disposition of the Containers: The dishes are sealed with sterile petrolatum and placed in an incubator, where they remain at 37 C. Most of them are left there for twenty-four hours, but some for thirty-six, forty-eight or fifty hours.

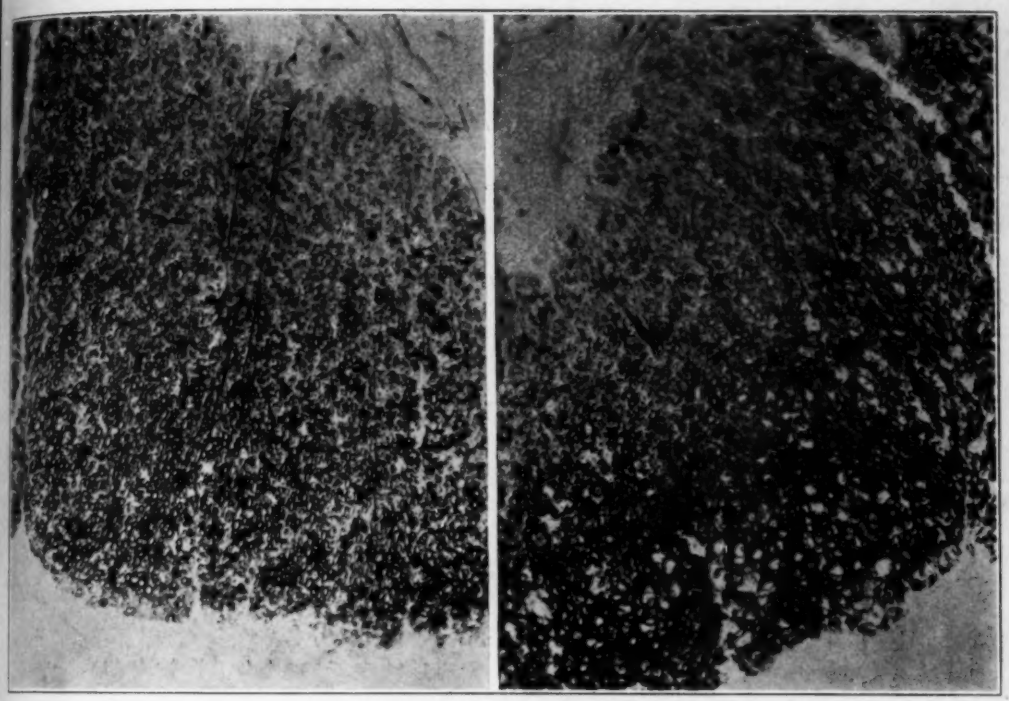

Fig. 1 (experiment 114).—Large lacunae are present in the cord treated with diseased plasma (right). Disarrangement and running together of myelin from different sheaths, with the formation of a dense mat, are illustrated in the same section. Also note the variations in the size of the lacunae (swollen sheaths) in the right section as compared with the left. Reduced from a magnification of 220. Figures 1 to 5 are of sections of rat spinal cords which were incubated in plasmas from normal persons and from patients with multiple sclerosis, respectively. That from the normal specimen is always on the left, and that from the diseased blood on the right. The contrast between the two is distinct in each instance. All have been prepared by the Weigert-Pal method.

5. Ultimate Care of the Specimens: On removal from the incubator, the cords are lifted out of the plasma with a spatula and put into the appropriate fixing fluid. They are then prepared by the hematoxylin and eosin, Marchi or Weigert-

Pal methods, after being embedded in celloidin. Every step in fixing, mordaunting and staining is identical for normal and diseased specimens.

6. Sectioning the Specimens: Twenty sections are cut from the end of each block; these are grouped as "no. 1." The next thirty-five sections are "no. 1 *A*"; the next fifty are "no. 2," and these are the ones mainly used for study. The remainder of the block is completely cut into about fifty sections, called "no. 3."

7. The Marchi sections were 15 and all the others 25 microns in thickness. It should be mentioned that the procedures make it impossible to secure successful frozen sections.

8. The rats used were all approximately 1 year old and were evidently in normal condition.

9. Fixation in Formaldehyde Prior to Experiment: In some instances, at the suggestion of Dr. Cornwall, the spinal cord was cut up as described, and the

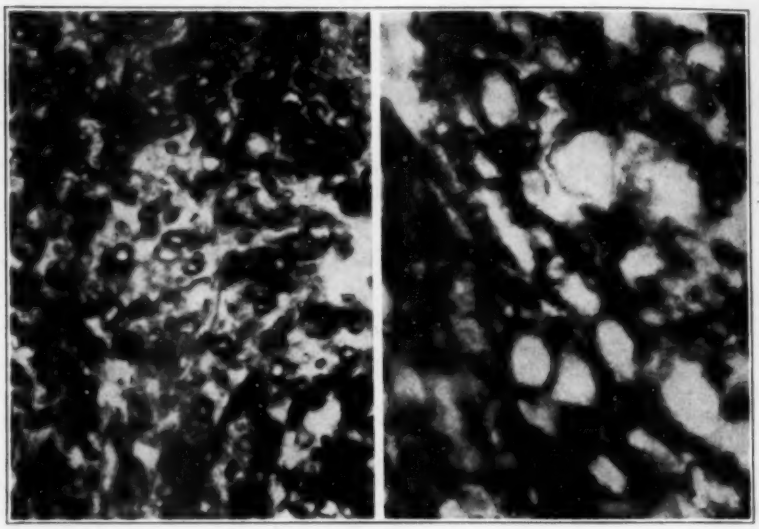

Fig. 2 (experiment 111).—The lacunae or swollen sheaths are evident in the section on the right (treated with diseased plasma) as contrasted with the normal section. Variation in the sizes of the sheaths is evident in the same section. The dense parts in the upper right segment (right section) show thickening of the walls of the sheath (without the usual swelling and lacunarization) and matting together of myelin from different sheaths. Reduced from a magnification of 900.

pieces were fixed in 10 per cent commercial formaldehyde for from eighteen to twenty-four hours before immersion in the plasma. As will be seen, this procedure gave particularly valuable results.

RESULTS

A special difficulty was encountered in examining the sections. Practically nothing is known about the staining variations in myelin which has been degenerating for only one day, and it was necessary

to learn, from sections, what changes to expect. The most pronounced alterations are as follows: (1) general disarrangement and disorganization of the pattern made by the myelin sheaths as they appear in cross-section (figs. 1, 3, 4 and 5, right); (2) swelling of the myelin sheath, which, in cross-sections, gives the appearance of large unstained lacunae by all the methods used (figs. 1 to 5, right); (3) thickening of the sheath, with increased density of stain by the Weigert-Pal method (figs. 1 to 5, right and left); (4) running together of myelin from different sheaths, so that in Weigert-Pal stains, dense black mattings are seen (figs. 1 and 4, right); (5) fragmentation of sheaths (fig. 6); (6) great variation in size of sheath (figs. 1 to 5, right); (7) formation

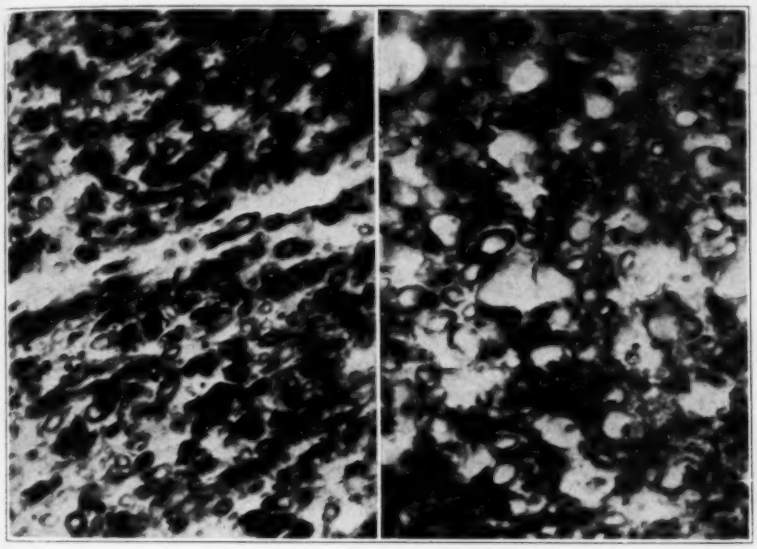

Fig. 3 (experiment 100).—Moderate lacunarization is illustrated in the figure on the right. One also sees groups of undistended sheaths with walls that are thickened and matted together, and moderate variation in the sizes of the sheaths. Reduced from a magnification of 900.

of scattered globules which still stain black by the Weigert-Pal method; (8) in no case severe damage of every sheath; the degree of change varies from sheath to sheath, and frequently entirely normal looking ones are encountered.

The effects, therefore, are shown mainly as changes in the form and arrangement of the myelin sheaths and only slightly as differences in stain-taking capacity.

Most of the myelin still stains by the Weigert-Pal method, even at forty-eight hours. The Marchi stain is not strongly positive at twenty-

four hours, yet the diseased specimens are usually blacker than the normal ones.

As can be seen in figure 1, the modifications are obviously due to the presence of a substance which has come into the cord from the outside; one usually sees that the peripheral half of the white matter is damaged to a far greater extent than the central half. Moreover, the myelin in close proximity to the ventral fissure, to an occasional accidental gross tear and to nerve roots which course through the white matter is usually greater than elsewhere. The alterations I speak of cannot be referable to autolysis, since in that case they should be more uniformly distributed. The postmortem factor is further excluded

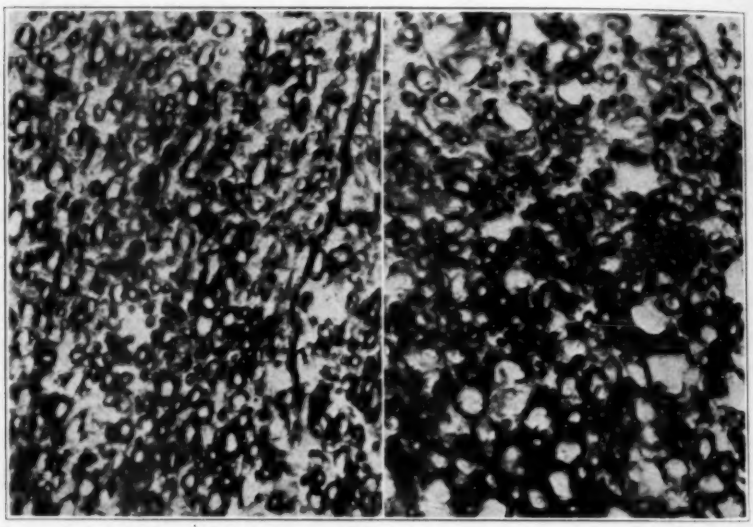

Fig. 4 (experiment 114).—Same cords as in figure 1, under higher magnification (reduced from a magnification of 900). The contrast between the specimens from the normal and the diseased plasma is more pronounced, and the various details of alteration are shown in greater detail.

by the cords that were utilized after fixation in formaldehyde (Dr. Cornwall); in these the distinction between disease and normal specimens is even sharper.

Naturally, it must not be anticipated that the cords incubated in normal plasma will be entirely free from alteration. They, too, are damaged, but to a much less extent and in much smaller areas than those from diseased plasma. The changes are of the same type in both, as might be expected. Therefore, what one must seek is a difference in degree rather than in type of change between normal and diseased plasma.

COMPARISON OF SPECIMENS FROM PLASMA FROM NORMAL PERSONS AND PATIENTS WITH MULTIPLE SCLEROSIS [1]

In the majority of cases, the chief differences between the normal and disease specimens lay in a great abundance of lacunae, with general disorganization in the disease specimens (figs. 1 to 5, right). This was demonstrated by all the methods used. In some, however, lacunarization fell into the background, and disorder and granularization were the essential points of contrast. In addition, differences were occasionally shown mainly by fragmentation of sheaths (fig. 6) and rarely by inability of the disease myelin to take the Weigert-Pal stain. The Marchi specimens, moreover, revealed slightly, but regularly and definitely, a greater blackness in the sections from multiple sclerotic than those from normal plasma.

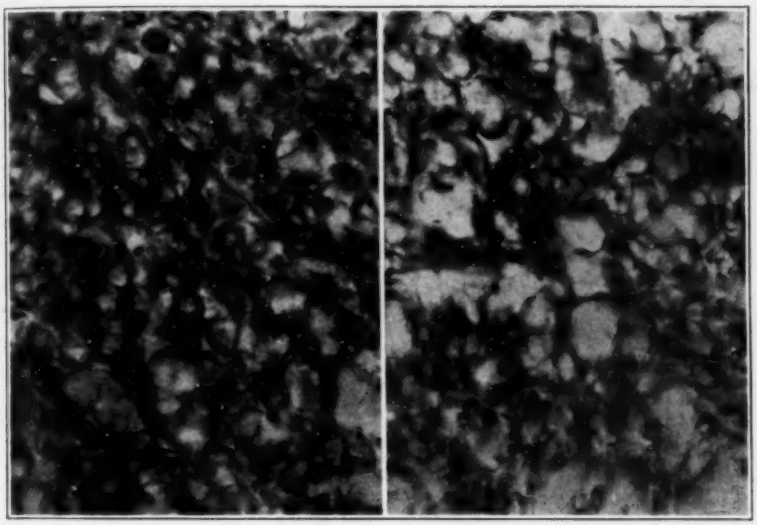

Fig. 5 (experiment 104).—The lacunarization is well seen. General disarrangement and variation in the sizes of the sheaths are also evident. Oil immersion lens. Reduced from a magnification of 1,400.

It is of the greatest importance to any one engaged in work of this type to appreciate the implications and complexities of any attempt to derive information from myelin. So intricate a mixture is myelin that one fraction of it may undergo the most marked changes, while the rest may perhaps remain unaltered. The disintegration of one fraction may give an appearance quite different from that of another fraction.

1. Three of the normal blood specimens were accidentally injured. In two of these instances the disease sections were checked against ten other normal sections, selected at random, and the contrast was striking. In the third, the damage to the sclerotic section was extreme.

The significance of the common stains used for normal and degenerated myelin is not fully understood and an attempt to speculate about them is likely to lead to error. Obviously, there is no quantitative means of studying myelin. One is therefore compelled, in a study such as the present one, to devise methods by which to utilize such knowledge of myelin as is available and to make empiric use of stains with which one is most familiar. One cannot be certain, within the first twenty-four hours, whether an unusually light or an unusually deep Weigert-Pal stain bespeaks greater myelin damage. It may also happen that

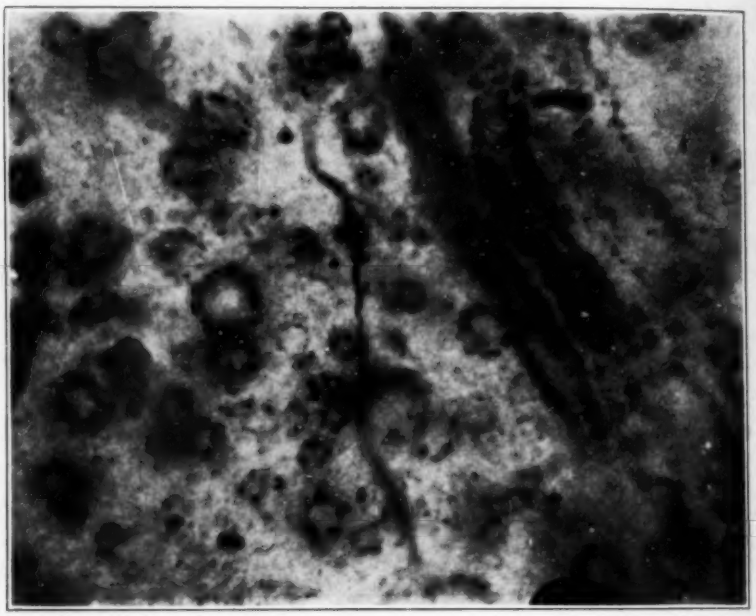

Fig. 6 (experiment 3).—Cord from a diseased plasma. Fragmentation of sheaths, of both the column fibers and the anterior roots, is distinct. Note also that many sheaths are entirely unstained. Oil immersion lens. Reduced from a magnification of 1,350.

difference in depth of stain may accentuate or cloud changes in myelin form.

Therefore, it cannot be denied that the best method obtainable at present is likely to be relatively crude in comparison with many now in general use for other purposes, such as chemical estimations of the blood. Any effort to study the properties of myelin must necessarily be beset with difficulties, but such facts as these need not deter one from attempting to study myelin. It seems certain that if proper care is taken, well defined results can be obtained. Under the circum-

stances it is necessary to be even more than ordinarily cautious in the interpretation of the observations.

Because of gross anatomic variations in the dorsolateral regions, it was found that the anterior and anterolateral columns were the most suitable for study. The fibers streaming across the ventral gray matter

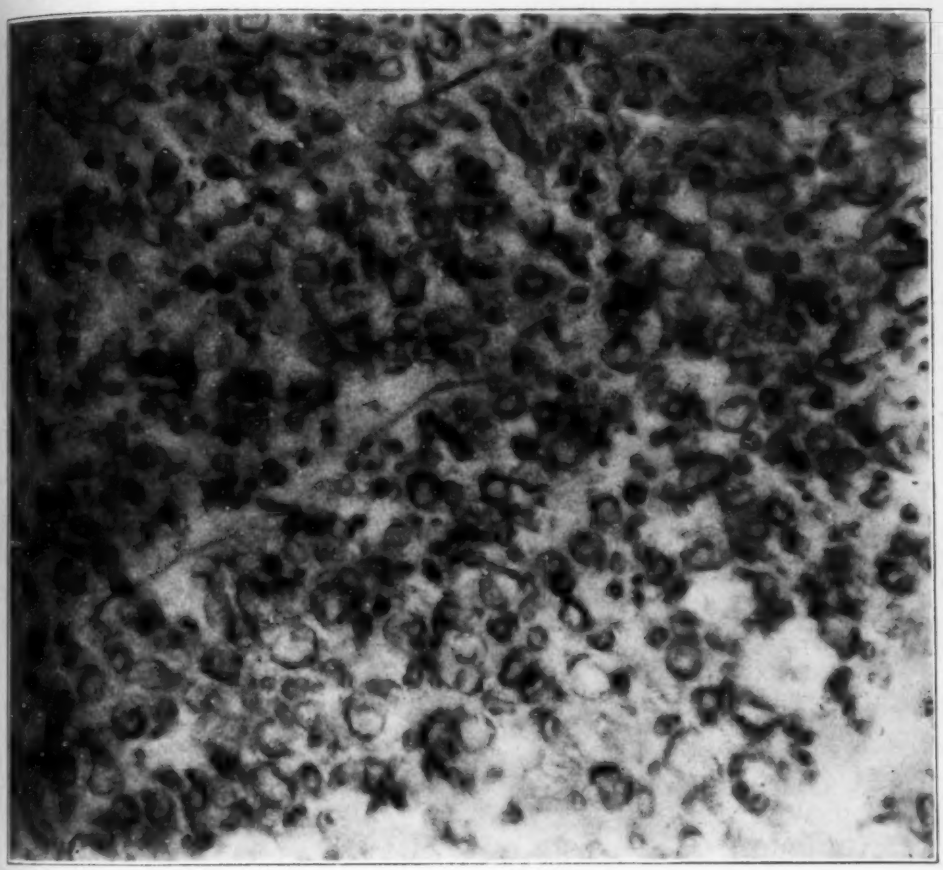

Fig. 7.—A normal spinal cord of a rat on which no experiment was performed.

are also well adapted, and show consistent differences between cords treated with normal and diseased plasmas.

When sections from the centers of the cords treated with the two types of plasma were compared, it was found, in thirty-seven of forty-two experiments, that the one treated with the diseased blood showed decisively a greater degree and area of damage; one could be distinguished from the other even when the specimens were unlabeled. Two of the remaining five examples were doubtful and three showed slightly

less destruction with the diseased than with the normal blood. Positive results were obtained from all seventeen cases.

An attempt was made to give grades to the degrees of difference between the sections treated with normal and diseased blood. While

TABLE 1.—*Results by Experiments*

Total number of experiments		42
Total number of positive results		37
Of these, total number	4+	17
	3+	4
	2+	7
Slight but definite		9
Total number of negative experiments		5
Of these, questionable result		1
Damage in normal equal to that in diseased blood		1
Damage in normal greater than that in diseased blood	4+	0
	3+	0
	2+	1
Slight but definite		2

TABLE 2.—*Results by Cases: Average of Results of Experiments Done in Each Individual Case*

Amount of Damage	Number of Cases
3+ to 4+	8
2+ to 3+	4
1+ to 2+	3
0 to 1+	2
Total	17

TABLE 3.—*Damage to Cords Treated with Plasma from Normal Persons and from Patients with Multiple Sclerosis as Compared with Absolutely Normal Cords*

Sections from Plasma from Normal Persons		Sections from Plasma from Patients with Multiple Sclerosis	
Degree of Damage	No. of Cases *	Degree of Damage	No. of Cases
0	3	0	0
0 to 1+	3	0 to 1+	0
1+	15	1+	2
2+	11	2+	9
3+	5	3+	10
4+	2	4+	21

* The total number of normal cases is short by three, as previously explained.

these figures are, of course, not the product of quantitative computations, they are useful in estimating the character of the results.

All the sections treated with normal and with sclerotic plasmas were also compared respectively with sections from an absolutely normal cord in order to determine the amount of "absolute damage" in each—that is, the degree by which each differed from a cord on which no experiment had been performed. The results are given in table 3.

COMMENT

Differences in Reaction of Myelin in Various Parts of the Nervous System.—It was consistently noted that the greatest changes occurred in the sheaths of the white column fibers; next came the fine fibers that stream across the ventral part of the gray matter and last the ventral nerve rootlets and nerves themselves. The conclusion seems justified, therefore, that myelin is varyingly constituted in different parts of the nervous system of the rat, and, if this condition is the same in man, it may have much to do with the evident selectivity of locus of so many diseases of the central nervous system.

Relationship of these Observations to the Pathogenesis of Multiple Sclerosis.—The conditions of the experiments are artificial, yet the procedures in both parts of every experiment were identical to the smallest detail of staining. The myelin used was not from human beings. However, marked destruction of rat myelin has been consistently demonstrated in cords immersed in oxalated plasma from patients with multiple sclerosis, and it therefore seems fair to hypothesize that the blood from such patients contains a myelinolytic factor or condition. Whether or not that factor is the cause of the destruction of myelin in the disease cannot be definitely stated, but this would be the logical deduction. The modifications in the specimens from normal plasma suggest that there may be there, too, a myelinolytic element—possibly the same one that occurs in blood from patients with multiple sclerosis—but there is strikingly less of it. The nature of the myelinolytic element is at present unknown and will be the subject of further study.

Other Diseases.—The experiments carried out so far have concerned mainly multiple sclerosis. Enough data are not yet accumulated to show whether other pathologic conditions are associated with the same observations. It may be said, however, that in two cases of postencephalitic paralysis, one of amyotrophic lateral sclerosis and one of pernicious anemia with changes in the spinal cord, no similar alterations were found.

Relationship of these Experiments to Diagnosis and Treatment of Multiple Sclerosis.—The method used is not like a colorimetric experiment in which quantitative results may be obtained relatively quickly. Six weeks are required for the completion of each test, and then there is no absolute standard by which to measure the conclusions. It may be that additional work will provide a nonhistologic technic with which accurately measured results can be secured promptly. At present the method cannot be recommended as a diagnostic test for multiple sclerosis and possibly allied diseases.

The experiments are by no means sufficiently advanced to suggest a specific treatment for the disease. Certain hypotheses, however, have initiated some attempts at treatment, the results of which should be mentioned. It was considered likely that the blood factor might turn out to be enzymatic, and, if such was the case, a lipase. Since quinine is known to be an inactivator of certain blood lipases, this drug was administered to eight badly crippled patients. In two of them there was no result. Five entered fairly complete remissions within from ten to fourteen days, and one was somewhat improved. Though these instances are reported, no therapeutic claims have been made. Multiple sclerosis is too treacherous a condition to permit the making of assertions for any remedy unless a large number of cases are tested. Even then, some standards of success must eventually be adopted. It would seem reasonable to demand of any therapeutic attempt that it produce, consistently, definite remissions within a relatively unvarying period of time. The symptoms and signs should probably be divided into two groups: those of such long standing that heavy scarring has probably occurred, leaving little hope of return of function, and those of more recent development, which might more reasonably be expected to recede. At all events, the later symptoms should disappear first.

SUMMARY AND CONCLUSIONS

1. A method is described by which myelinolysis is produced in vitro in the spinal cords of rats by oxalated plasma from patients with multiple sclerosis in much greater degree than by similar plasma from normal subjects.

2. Description is given of the appearance of myelin in the first twenty-four hours of degeneration, with Marchi and Weigert-Pal stains.

3. Myelin varies in constitution in different parts of the nervous system of the rat. This may have a bearing on the selectivity of localization in some diseases.

4. Some observations on patients with multiple sclerosis treated with quinine are mentioned.

TUMOR OF THE BRAIN WITH SUDDEN ONSET OF SYMPTOMS

A REPORT OF TEN CASES AND REVIEW OF SIMILAR REPORTS *

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For years it has been recognized that glial tumors vary in histologic structure. Of this heterogeneous group, Strauss and Globus called attention to one type first called spongioblastoma and later spongioblastoma multiforme. In their report [1] in 1918, they stressed the frequently sudden onset of symptoms, the unusually rapid progress and the fatal termination and reviewed the past varying conceptions of the histology and derivation of brain tumors. The histologic features were summarized as: (1) the neuro-epithelial character of the dominating type of cells; (2) the presence of well defined spongioblasts and ependyma cells; (3) the syncytial structure alternating with reticular interlacement of cell processes, and (4) the marked proliferative tendencies.

Clinically, this type of case offers much difficulty in diagnosis with the sudden onset, variable symptomatology and rapid progress, as evidenced in a number of cases here reported and reviewed, in some of which, particularly, the rapidity of the onset and progress and the size of the tumor were startling.

REPORT OF CASES

CASE 1.—*Clinical History.*—A white man, aged 50, was admitted, March 1, 1925, to the medical service of Dr. Riesman, in the Philadelphia General Hospital, complaining of gaseous distention and giving an entirely inaccurate history. His brother, however, stated that six weeks before, the patient began to act queerly while at work in a greenhouse; his employers wanted him to quit work for a while as a memory defect was noticeable. He remained at home for about one month, during which he spent much time walking about the house and putting pieces of paper in flower pots as if he were setting out plants. Enunciation was not affected, but his conversation became more and more unintelligible.

* Submitted for publication, Oct. 14, 1929.

* Read at a meeting of the Philadelphia Neurological Society, May 24, 1929.

* From the Neuropathological Laboratory and Wards of the Philadelphia General Hospital, and the Neurological Department of the Graduate School of Medicine of the University of Pennsylvania.

* The pathologic work was done by Dr. N. W. Winkelman, neuropathologist to Philadelphia General Hospital.

1. Strauss, I., and Globus, J. H.: Neurol. Bull., July, 1918.

Examination.—On admission to the hospital, the patient was disoriented as to time and place; memory was distorted; consciousness was clouded; he took no interest in his surroundings and did not speak spontaneously, though his speech was unimpaired. There was some tremor of the hands in performing finer movements, and his handwriting suggested paresis. A marked recent optic neuritis was present. The roentgenogram of the skull was normal.

Course.—The symptoms progressed; the tremor of the right arm increased and he had to be fed, though he took food well. Food collected in the right cheek, and a large bolus needed to be removed frequently, though there was no apparent facial weakness. The deep reflexes were exaggerated on the right, and he presented a right Babinski sign, with no other localizing symptoms. March 29, he had an epileptiform seizure, with flexion of the left arm and leg, and rigidity and clonic contractions of the right side, beginning in the right hand and arm, the eyes deviating to the right. The optic disks were definitely choked. Coma followed a series of convulsions and the patient died that same evening.

Brain.—On separation of the cerebral hemispheres, an evagination of the right frontal lobe into the left was noted in that portion of the mesial surfaces anterior to the corpus callosum. Immediately above the right olfactory tract and bulb there was a grayish, round elevation, 2 cm. in diameter, and posterior to this and anterior to the optic chiasma was a protruding growth 1.5 cm. in diameter. There was also a bulging of the third ventricle in the interpeduncular space. On vertical sectioning, an immense, yellowish, blood-speckled neoplasm was revealed, which involved both frontal lobes in their central portions, the right more than the left, leaving only a comparatively narrow peripheral border intact. It was rather sharply demarcated, completely destroyed the corpus callosum and wholly obliterated the right lateral ventricle. Posteriorly, the neoplasm decreased in size, involving less and less of the left hemisphere, until it stopped abruptly in a vertical plane which passed through the most posterior part of the interpeduncular space.

Microscopically, the tumor was made up of a necrotic center surrounded by a highly loose areolar tissue in which were present glial cells of various forms: ameboid, spider, gitter and rod-shaped.

Diagnosis.—The diagnosis was glioma, spongioblastoma multiforme.

Case 2.—*Clinical History.*—A white man, aged 66, was admitted to the service of Dr. Potts at the Philadelphia General Hospital, July 13, 1926, with a history of a coughing spell followed by a "stroke," on the Saturday preceding July 4. He lost control of his hands and feet, was delirious, talked foolishly and mixed his words. The day before admission, he had another stroke; the patient stated that he awoke one morning to find his face drawn to one side. The past history was unimportant except for occasional frontal headaches and bronchial asthma during the preceding six months. He had been a chronic alcoholic addict.

Examination.—There was marked emaciation, with slightly irregular pupils, left facial weakness and impairment of enunciation and deglutition. He was irrational at times and disoriented. He lapsed into coma and died, July 22. The colloidal gold curve was 5555433210.

Brain.—Examination showed a granular softening in the right temporal lobe, which on section revealed a neoplasm extending from the second vertical section through the lower half of all sections of the right frontal lobes to the juncture of the parieto-occipital regions. It extended in depth to the basal ganglion region, was roughly oval and measured 5 cm. in cross-section. Microscopically, the

tumor presented several different structures, apparently indicating the mode of origin and rapid loss of differentiation of the tumor cells. Some sections showed large ganglionic cells, from these seemed to be derived large spider cells. The cellular portions were entirely lacking in any neural qualities and were most actively growing.

Diagnosis.—A diagnosis of spongioblastoma multiforme was made.

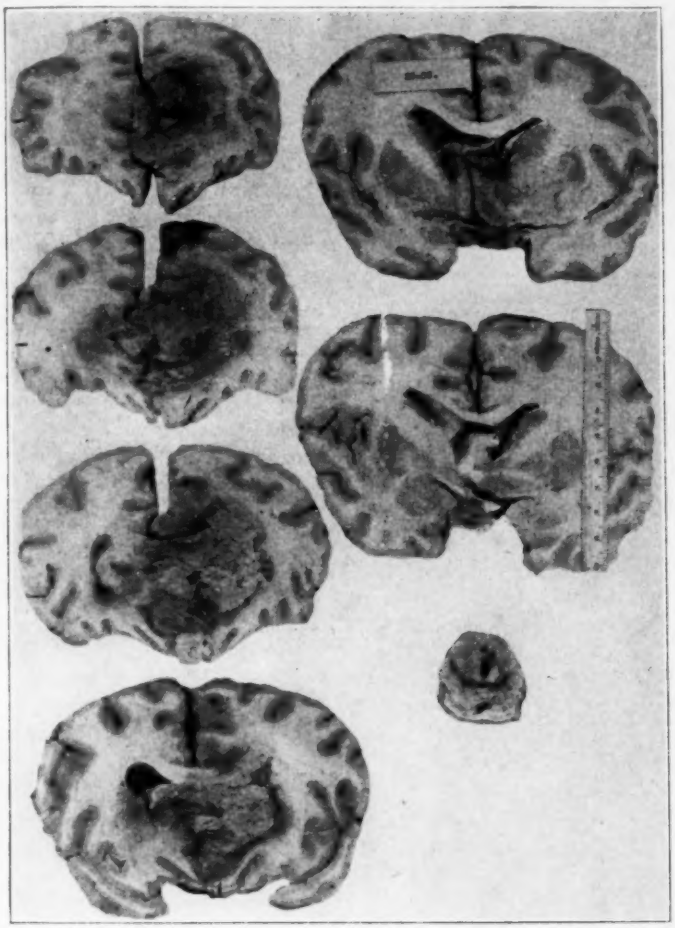

Fig. 1 (case 1).—Vertical sections showing neoplastic involvement of both frontal lobes in their central portions, leaving only a comparatively narrow peripheral border, completely destroying the corpus callosum and obliterating the right lateral ventricle. The process decreases posteriorly till it stops abruptly in the vertical plane passing through the most posterior part of the interpeduncular space.

Case 3.—*Clinical History.*—A white woman, aged 50, was admitted to the Philadelphia General Hospital, in the service of Dr. Petty, Nov. 22, 1926, complaining of weakness of the legs. Three days previously she had suddenly become unable to move her legs, and while walking home fell and could not rise. For

two months before this time, she had had a slight throbbing headache, some palpitation and slight weakness of the legs.

Examination.—The patient was very obese, weighing about 200 pounds (90.7 Kg.). She was mentally clear when admitted to the hospital. The reflexes in the upper extremities and in the right knee were normal, the left knee jerk was much diminished, and the achilles jerk was absent on both sides. There was about 50 per cent loss of power in the legs. There was no Babinski sign or ankle clonus, and sensation was normal. The urine showed sugar and a faint trace of albumin. The sugar content of the blood was 243 on November 26; 251, the next day; and 183 on November 29. On December 26, the patient became stuporous, and she died the next afternoon with hypostatic pneumonia. The neurologic diagnosis was left cerebral thrombosis with hemiplegia.

Brain.—The brain was small, weighing only 1,110 Gm. The convolutions were much flattened as if under pressure, and congestion was marked. Frontal sections showed a dilated anterior ventricular system containing a yellowish fluid. The septum pellucidum was the seat of a nodular, bluish mass hanging in the median line. In a section about 1.5 cm. posterior, the tumor was seen to be attached to the undersurface of the corpus callosum and was hemorrhagic. On the left side, another mass was present which involved the entire caudate nucleus and the anterior limb of the internal capsule. About 2 cm. behind this the tumors were of the same appearance on the two sides, the one on the left invading the entire basal ganglion, and the one on the right the white matter more than the ganglion. The tumor masses extended back into the occipital region.

Microscopically, the structure of the tumor was very fibrous, but there were numerous cells in places and few in others. The cell type consisted of a small round nucleus with considerable cytoplasm.

Diagnosis.—The diagnosis was glioma, spongioblastoma multiforme.

Case 4.—*Clinical History.*—A white man, aged 46, was admitted to the Philadelphia General Hospital, in the service of Dr. Burr, on Jan. 6, 1927, with a history of having become mentally dull three weeks previously. He would sit about for hours without uttering a sound, and was discharged from his position as an automobile accessory clerk on account of his dulness. He did not speak as clearly or as much as formerly. A week prior to the apparent onset of symptoms, he had been struck by a car. It was not known whether he was knocked down or not, but there was no evidence of injury to the head.

Examination.—On admission to the hospital the patient seemed confused but was not disoriented. He answered questions in a slow monotone, and the speech was somewhat slurred. A physical examination gave essentially negative results. Neurologically, he demonstrated an uncertain and unsteady gait, with a tendency to fall to the right and difficulty in swallowing, but with no other pathognomonic signs evidenced. Roentgen and ocular examinations and laboratory observations all gave negative results.

Brain.—The brain showed multiple neoplasms in both hemispheres. The first, 2 cm. in diameter, was located in the right frontal lobe. A larger mass occupied a large part of the corona radiata of the right hemisphere, and extended from the fourth to the ninth vertical sections. A third mass was present in the tenth and eleventh sections in the left basal ganglion.

Microscopically, the tumors were found to be moderately vascular and indistinctly marked off. The cells were not uniformly arranged, and areas were commonly found in which the cells were apparently collected into a zone, with a number of deep layers arranged about a homogeneous center of degenerated

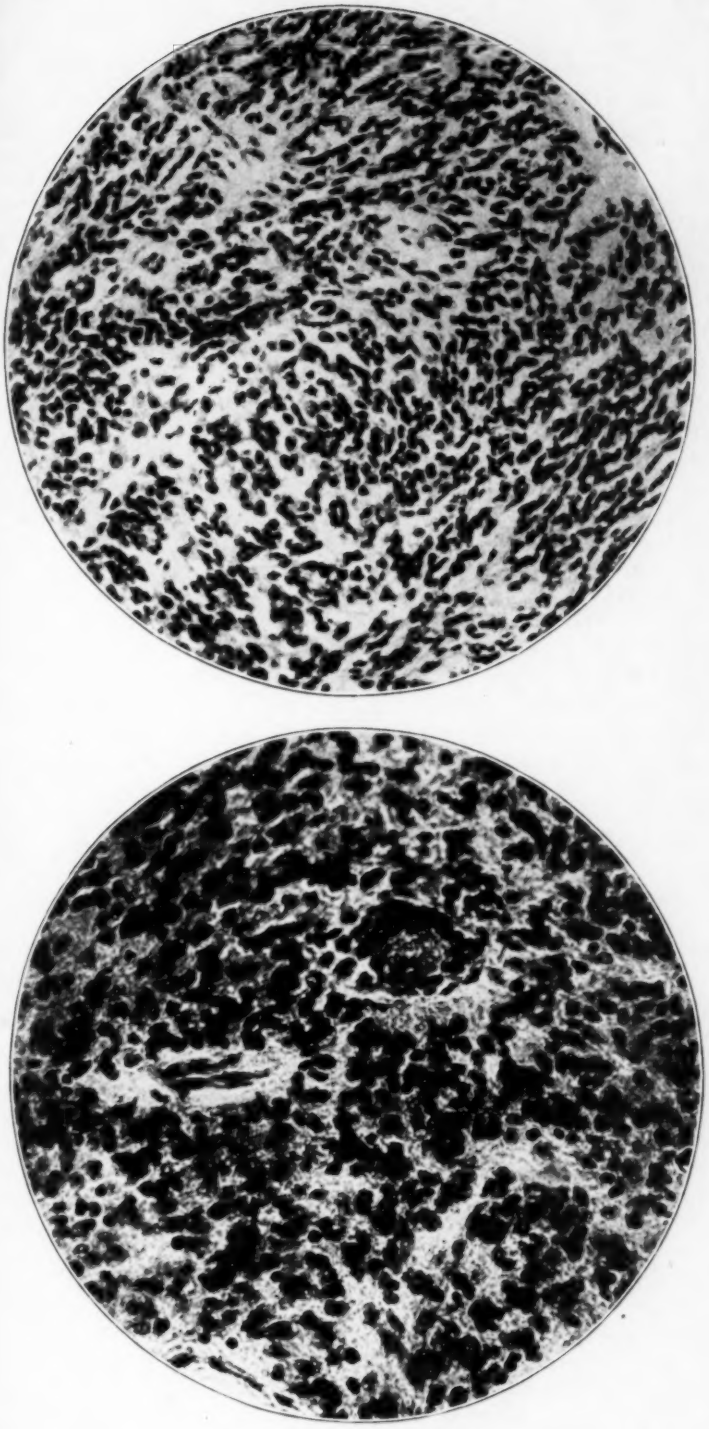

Fig. 2 (case 4).—Section showing lack of uniformity in cell arrangement. The cells are mostly spongioblasts with some giant cells in evidence.

tissue. The cells were mostly spongioblasts, but giant cells were commonly found. There were also areas in which cells were arranged like waves and presented a sinuous course.

Diagnosis.—The diagnosis was glioma, spongioblastoma multiforme.

Case 5.—*Clinical History.*—A girl, aged 21 months, in the service of Dr. Griffiths at the Children's Hospital, was under the observation of Dr. Leavitt during her illness beginning in October, 1927, with an attack of unconsciousness, in which she presented a generalized convulsion. There were no further symptoms until early in November, when the child became apathetic, began to vomit and complained of headache. The mental apathy deepened during the latter part of November and through December, so that she could scarcely be aroused. She had frequent and definite projectile vomiting.

Examination.—There were no localized paralyses of any cranial nerves or of the extremities. Examinations of the eyegrounds revealed increasing papilledema up to 8 diopters in both eyes, with retinal hemorrhages and blindness so far as could be determined. The spinal fluid was normal except for the pressure, which was increased to 22 mm. of mercury. No definite tests concerning cerebellar function were attempted as the child was so stupid that she would not obey commands and made no attempts to walk or to use the extremities for any purposeful movements.

Course.—Three weeks prior to death, a complete bilateral wrist drop and an incomplete bilateral foot drop occurred, which gave rise to the erroneous diagnosis of lead poisoning. The case had been diagnosed as tuberculous meningitis, encephalitis and tumor of the brain. The child died on Jan. 24, 1928.

Brain.—The brain presented general edema and an extreme degree of hydrocephalus with thinning of the cortex. The tumor was in the vermis of the cerebellum, in the midline, with its center at the roof of the fourth ventricle, which it had occluded as well as the aqueduct, producing an extreme degree of hydrocephalus. The tumor was cystic at its center and had ruptured, some of its gelatinous content being found along the anterior aspect of the brain stem. The cystic area was partially filled with hemorrhage. The tumor was in the midst of cerebellar tissue and consisted of an irregular collection of cells of a glial nature, with irregular oval nuclei and a tendency to palisade arrangement. The cytoplasm was fairly distinct, and no large cells such as giant cells were present.

Diagnosis.—Glioma, spongioblastoma, was diagnosed.

Case 6.—*Clinical History.*—A white man, aged 47, was admitted to the service of Dr. Potts on June 20, 1928, with the chief complaints of headache and drowsiness. He had been well until thirteen weeks before, when he rather abruptly became apathetic and was drowsy, falling asleep almost anywhere and being awakened with difficulty. He soon began to suffer from headaches, and he vomited twice, once at the onset of the illness and again four weeks before admission. He had been out of bed part of the time each day until four days before, but the last time he attempted to walk he ran about 50 feet before being able to stop; at times he had fallen in trying to walk. He had been incontinent the week previous to admission to the hospital, during which period he was somnolent and disoriented as to time. Though he had eaten moderately well, he had lost from 30 to 40 pounds (13.6 to 18 Kg.).

Examination.—A neurologic examination disclosed Argyll Robertson pupils, somewhat slurring speech and fair station but slight staggering when he attempted to walk. His face and tongue showed tremors. There were a slight ptosis of

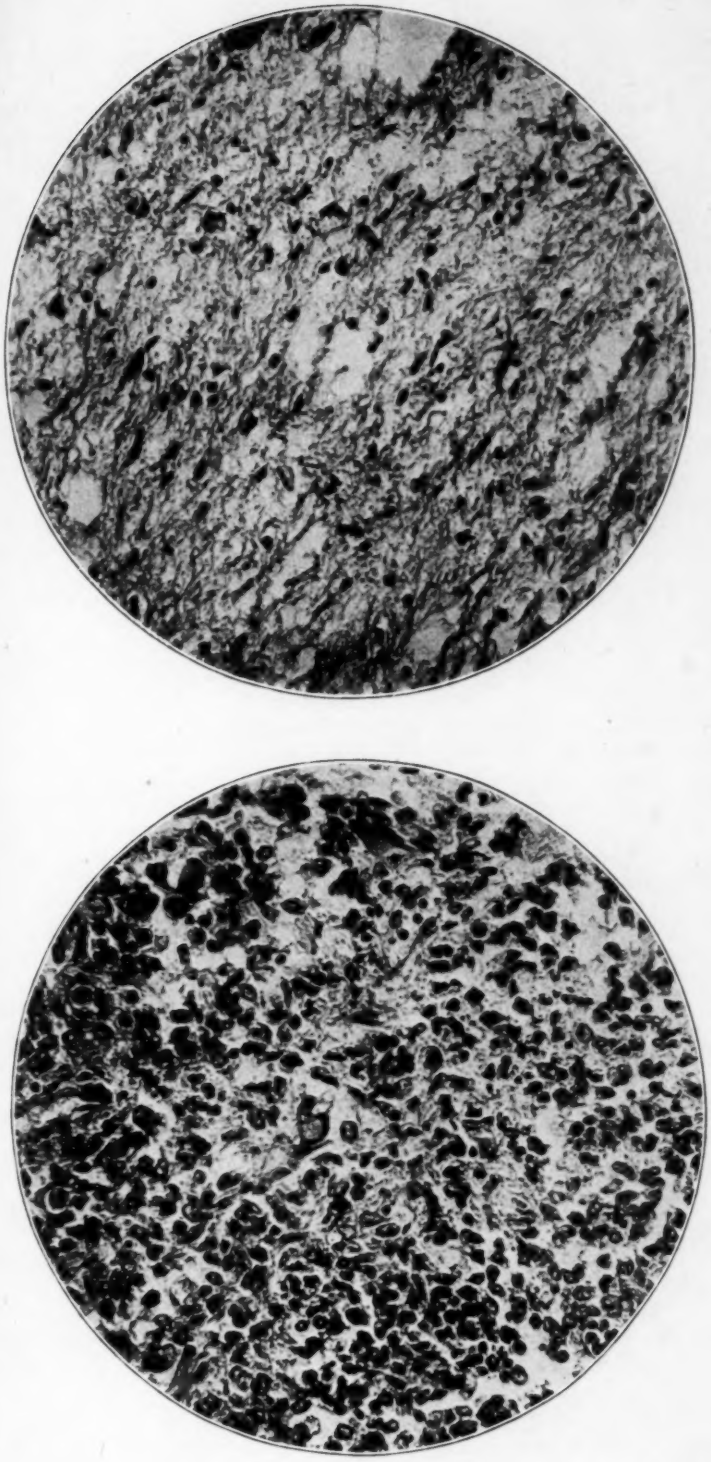

Fig. 3 (case 5).—Sections showing irregular collections of cells of a glial nature with irregular oval nuclei (tendency toward palisade arrangement).

the right eyelid and some smoothing out of the right side of the face. The fundi oculi showed from 4 to 6 diopters choking of both disks, with many large and small hemorrhages. The spinal pressure was 30 mg. of mercury in the prone position, and the Bárány test also demonstrated increased intracranial pressure, although an encephalogram gave no evidence of it. The laboratory observations were all normal except for one cerebrospinal fluid cell count (July 20, 1928) of 50.

Course.—On July 11, the patient was observed in a jacksonian attack, affecting the left shoulder girdle and the left hand and arm. Hearing became definitely impaired. July 13, Dr. Temple Fay performed a decompression over the right frontal area with removal of the bone flaps. The right ventricle was apparently obliterated, and the introduced cannula dropped of its own weight a distance of 5 cm., indicating a subcortical degenerated area probably in an extensive glioma. The patient died on Oct. 16, 1928.

Brain.—The brain presented neoplasms involving both hemispheres. The lesion on the right extended from the frontal pole to the vertical plane of the most posterior part of the corpus callosum. It soon enlarged so that it first involved the entire lower half of the right hemisphere and then extended into the upper half of the posterior part. The neoplasm on the left was first shown in the vertical plane where the lesion on the right ended, involving the whole central portion of the occipital lobe and extending through three vertical sections. On vertical sectioning the lesion on the right measured 2.5 by 1.5 cm., and in the middle third of the right hemisphere involved all of the brain, extending to the basal ganglion and destroying the putamen and globus pallidus, with compression of the internal capsule; it contained a yellowish material.

Microscopic section showed much coagulation necrosis, but at the margin was a tumor growth made up of polymorphous types of cells; the majority consisted of a fairly large round nucleus, with heavy chromatin granules, a definite cell wall and a pyriform shaped cytoplasm. Giant cells with two or more nuclei and homogeneous cytoplasm were to be seen. A tendency to palisade arrangement was evidenced with oval nuclei and the appearance of spongioblasts.

Diagnosis.—Glioma, spongioblastoma multiforme, was diagnosed.

Case 7.—*Clinical History.*—A white woman, aged 57, was admitted to the service of Dr. Allyn at the Philadelphia General Hospital, Nov. 18, 1928, with a history of a fainting spell five weeks previously in which she became dizzy and had to lie down. She was apparently well after this until three weeks later (November 7), when she fell unconscious and was found unable to speak or to use the right side of the body. From then on she grew progressively worse; she was admitted to the hospital in an extremely weakened condition, with Cheyne-Stokes respiration, and died without regaining consciousness.

Examination.—On admission there was a right-sided hemiplegia, with convulsive movements of the right arm and leg, aphasia and myocardial hypertrophy with a mitral systolic murmur.

Brain.—The weight was 1,450 Gm., with the left cerebral hemisphere definitely larger than the right. A circular mass, 3 by 4 cm. in diameter, was situated in the lower lateral portion of the left cerebral hemisphere in the temporofrontoparietal region. It consisted of homogeneous material, flecked with blood and yellow patches and one very firm, pearly white mass, 1 cm. in diameter, in its midst.

Microscopically, there were many thin-walled blood vessels. Under a high power lens the mass was seen to be made up of spongioblastic cells of various sizes and shapes, many of them showing engulfed cells and blood pigment. There were also many giant blood cells present.

Diagnosis.—The diagnosis was glioma, spongioblastoma multiforme.

CASE 8.—*Clinical History.*—A white man, aged 56, was admitted to the Philadelphia General Hospital, in the service of Dr. Bochroch, on Jan. 9, 1929, disoriented and somewhat deteriorated, forgetful and talking to himself. He had been drinking to excess for the past year until the sudden onset of the mental disorder, five weeks before, immediately after he lost his job.

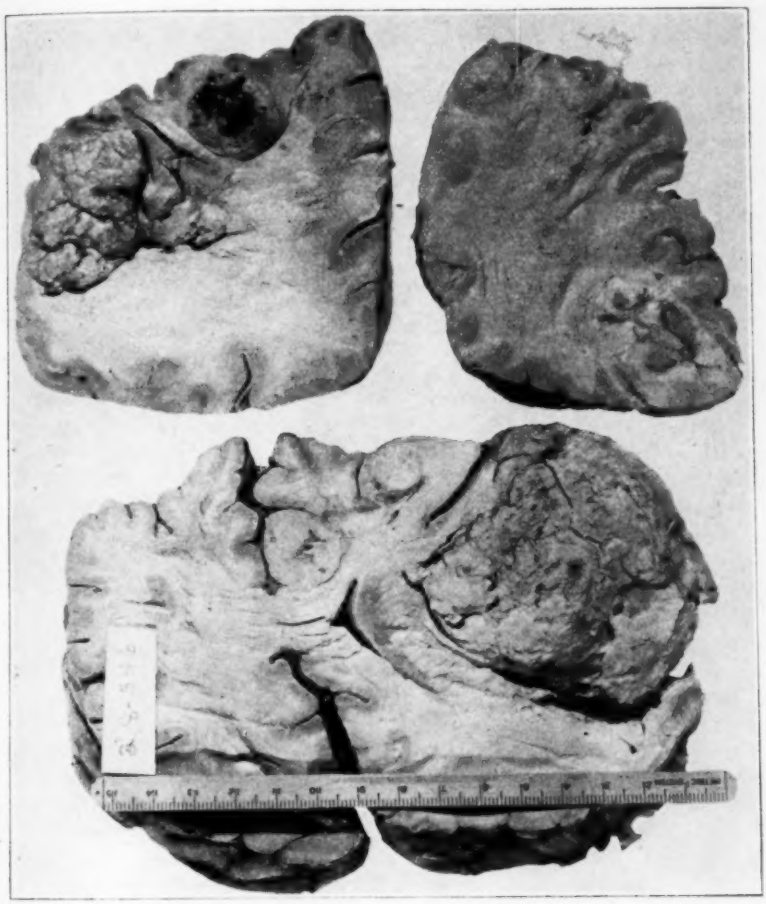

Fig. 4 (case 6).—Neoplasms involving both hemispheres. The lesion on the right extends from the frontal pole to the vertical plane of the most posterior part of the corpus callosum. The neoplasm on the left side is first shown in the vertical plane where the lesion on the right ends, involving the entire central portion of the occipital lobe and extending through three vertical sections.

Examination.—The patient was somewhat stuporous on admission, slow in reacting to requests and irrelevant at times. The pupils were unequal, the right being larger than the left; the right pupil was fixed, and the left was very sluggish in accommodation to light. The deep reflexes were all exaggerated, and the right extremities showed weakness but no evident paralysis.

Course.—A week later, the patient showed a distinct paralysis of the right side of the face, arm and leg, with a right Babinski sign, and he rapidly became stuporous and died eight days after admission. The case had been diagnosed as hemorrhage of the left middle cerebral artery, with ingravescent hemorrhage.

Brain.—Examination revealed a tumor, the size of a small lemon, in the tip of the left temporal lobe, extending into the substance of the brain, and invading the left peduncle and left occipital lobe. It was vascular and firm but showed fresh hemorrhage into its substance and a central area of degeneration necrosis and absorption. The brain weighed 1,700 Gm.

Microscopically, the neoplasm was made up of spongioblastic cells of various types, with numerous giant cells having peripherally arranged nuclei. In one part of the lesion a large hemorrhage with marked softening appeared.

Diagnosis.—Glioma, spongioblastoma multiforme, was diagnosed.

Case 9.—*Clinical History.*—A white man, aged 64, admitted to the Philadelphia General Hospital, in the service of Dr. McCarthy, on Nov. 30, 1928, had quit work three weeks previously on account of headache. Since then he had been drowsy and had slept most of the time, had been gradually losing strength and had difficulty with speech. He wrote the following letter to a sister: "My dear, I am in a letter. I am nibbed and nudder. Am bellen. Madden dear. Collendear." He had been a chronic alcoholic addict for years.

Examination.—The patient was confused and disoriented; he apparently understood conversation but had great difficulty in answering. His memory showed defects, and judgment was impaired. Physically, he appeared normal except for signs of senility. Neurologically, he showed some weakness of the hand grips and of both legs. The biceps and triceps reflexes were diminished, and the patellar and achilles jerks were absent. There was no Babinski sign or clonus.

Course.—A few days after admission, he became aphasic, and three weeks after admission, he was found to have lost all use of the right hand and leg and the ability to speak, although he obeyed commands. The tongue deviated to the right on protrusion, but there was no appreciable facial weakness or Babinski sign. Six days later, there was some recovery of power in the right hand, but no further change was noted until death from pulmonary edema, seven weeks after admission to the hospital, and about ten weeks after the onset of symptoms. The diagnosis was cerebral thrombosis, fairly well localized to the left frontal lobe in the region of the motor speech area, and arteriosclerosis.

Brain.—The brain showed the presence of a neoplasm, the size of a small orange, lying in the substance of the left occipital lobe, occupying most of the white matter and invading the gray. It extended from the posterior horn of the lateral ventricle to within 1 cm. of the occipital pole. Its center showed some degeneration and some recent hemorrhage.

Microscopically, the lesion was seen to be a very cellular neoplasm with spongioblastic cells of various forms arranged in rows. Marked areas of degeneration, softening with gitter cells and perivascular collections of round nucleated cells through the tumor were present.

Diagnosis.—The diagnosis was glioma, spongioblastoma multiforme.

Case 10.—*Clinical History.*—A white man, aged 59, following previous good health, suffered a generalized epileptiform seizure on Dec. 12, 1928, and was received in the service of Dr. McConnell at the Philadelphia General Hospital on Feb. 21, 1929. His first convulsion had lasted fifteen minutes and was followed by several hours of sleep. Two similar attacks occurred that evening. Following these he began to lose memory, and in January he was found unconscious beside his loom in the mill where he worked. The next day he had two unconscious

spells, and another on January 15. Following this date he complained of headache and vertigo, and his wife noticed drooping of the right side of the face with failure of emotional expression on the right side and weakness of the right arm. Gradually he lost ability to talk. He was able to write until January 20.

Examination.—On admission, the patient did not obey commands nor recognize written words. He could not write or copy a written sentence, and simple written words could not be interpreted. A neurologic examination disclosed unequal, irregular pupils reacting sluggishly to light; the face drawn slightly to the left and a slight increase of the deep reflexes in the right lower extremity. There was no Babinski sign or ankle clonus, but a marked tremor of both hands, more marked in the right, was noted.

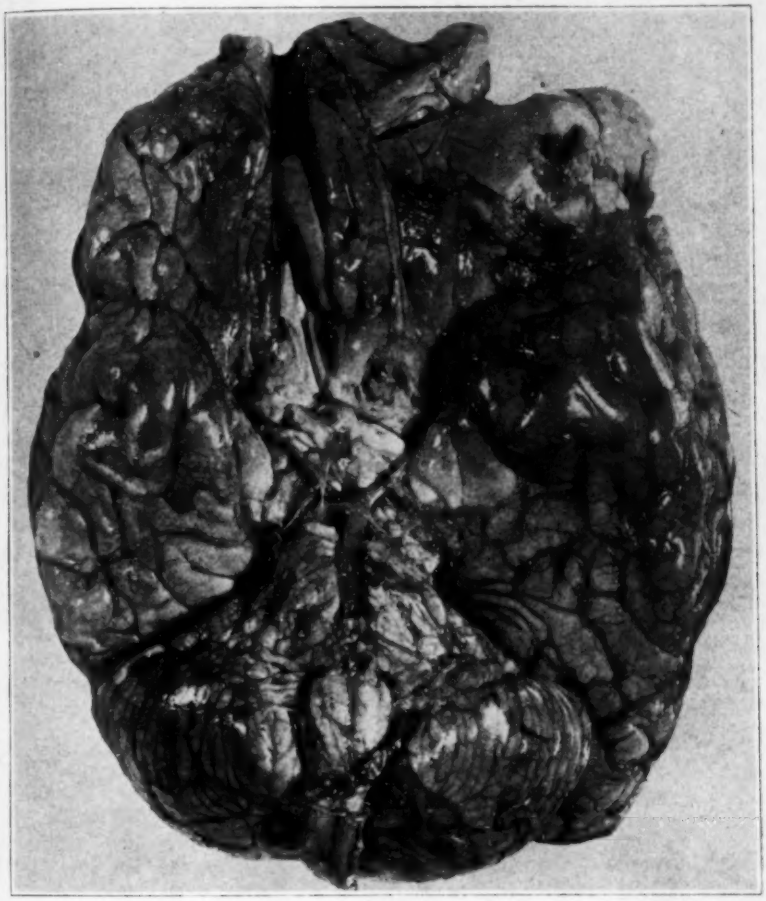

Fig. 5 (case 10).—Enlarged left hemisphere pushed over toward the right side. The left temporal lobe is pushed downward and toward the median line with a marked compression of the olfactory nerve and compression with distortion of the optic tract.

Examination of the fundi showed gray disks with temporal conus, marked arteriosclerosis and tortuosity of the smaller vessels. Station and gait were normal. The speech deficiency was marked. The patient seemed to try hard to concentrate in an effort to answer questions, frequently carrying out a definite series of movements: first he would make facial grimaces; then with his left hand he would stroke the left side of the face and the back of the head and then his chin with his fingers. This might be followed by some answer, but more frequently by failure. He showed a spontaneous apraxia. The spinal fluid was clear and under 22 mm. of mercury pressure; it showed a trace of globulin and

Fig. 6 (case 10).—Section through the hemispheres showing the hemorrhagic, necrotic, infiltrating tumor extending down toward the orbital surface and back into the temporal lobe over the left caudate and thalamus.

gave a colloidal gold curve of 3443332100. Other laboratory tests gave negative results.

Course.—On March 4, while eating, the patient fell to the floor, but returned to bed unaided. He became more intractable and irrational from this time on. On March 18, an encephalogram, made by Dr. Grant, showed a pushing of the left ventricle to the right; the next day a craniotomy was performed, and a sense of resistance was encountered in the left frontotemporal region about 2 cm. below the surface; the patient's condition was too unfavorable to permit a continuation of this procedure. He did not regain consciousness, and died the next day.

Brain.—The brain showed an enlarged left hemisphere which pushed over toward the right side. The left temporal lobe was pushed downward and toward the median line with a marked compression of the olfactory nerve and compression with distortion of the left optic tract. Section through the frontal lobe showed a hemorrhagic, necrotic, infiltrating tumor extending down toward the orbital surface and back into the temporal lobe over the left caudate and thalamus.

Microscopically, the tumor was extremely cellular in parts, with a large part necrotic, intense fibrosis around areas of necrosis and softening; it contained numerous phagocytic cells. In the well preserved areas characteristic medulloblasts were seen, with enormous numbers of mitotic figures arranged in small, illy defined groups.

Diagnosis.—The diagnosis was glioma, medulloblastoma.

SUMMARY

The age incidence in the ten cases here reported ranged from 21 months to 66 years, with an average age of 50 years. The duration of illness from the onset of symptoms till termination by death was from three weeks to three months, with an average of forty-four days, excepting in one patient who lived seven months, four months of which followed a decompression; this brought the complete average of duration to sixty days. The symptoms in these cases were ushered in by an attack of unconsciousness in two, mental confusion in two, sudden paralysis in two, a convulsion in one, headache with speech defect in another and apathy and headache in one.

The location of the neoplasm was in the frontal lobes in two, included the frontal and temporal lobes in two, and in one each was found in the temporal lobe, the occipital lobe and the vermis of the cerebellum. Three of these cases presented multiple lesions; in one tumors were found in both cerebral hemispheres and the basal ganglia; in another in the left frontal and occiptal lobes, and in the third in both frontal lobes.

Microscopically, all the tumors were of the spongioblastoma multiforme type except in case 10.

COMMENT

In the Transactions of the American Neurological Society, 1924, is included a report of sixteen cases of this type of tumor of the brain by Globus and Strauss.[2] Nine were in male patients and seven in female, the ages varying from 5 to 65 years, and averaging 40. The prominent initial symptom noted in eight of these cases was headache —combined with vertigo in three, with mental confusion in one, with lapse of memory in another and with inability to walk in one. The onset in two was initiated by a generalized convulsion and in one by jacksonian attacks after headache. Two patients first noted their dis-

2. Globus, J. H., and Strauss, I.: Tr. Am. Neurol. Soc., 1924.

order as beginning with blurred vision—in one of them combined with pain in the eye and headache, and in the other with irritability and garrulousness. In two the onset was demonstrated by speech difficulty and weakness of an arm. A cervical case began with pain in the back of the neck and tenderness and stiffness of the neck as the first signs. The average duration of illness in this series was one hundred and five days from the initial symptom till death. As to location, eight were found in the frontal lobes, two each in the frontoparietal and temporal areas and one each in the parieto-occipital region, in the basal ganglia, in the cerebellopontile angle and in the cervical region of the cord. Two of these presented multiple lesions.

Wilson and Winkelman [3] reported seven cases of tumors of the brain with sudden onset of symptoms in 1925. Five of their patients were men and two women, aged from 39 to 66, with an average age of 48 years. An onset with mental confusion as the prominent symptom was presented in four patients, being combined with vertigo in one, with headache in another, and with stupor in a third. Headache and stupor were the prominent initial symptoms in the other cases. The duration of illness averaged seventy-four days, varying from seven days to as many weeks, except in one patient who lived four months after the first symptom. Four of the tumors were in the frontal lobe and two in the temporal; one was located in the parieto-occipital region.

Recently Elsberg and Globus [4] reported a series of thirty-seven cases of tumor of the brain in twenty-five men and twelve women of an average age of 45. The average time from the onset of symptoms till admission to the hospital was from seven days to four months, averaging seventy-six days. Headache, often severe, was given as the most common initial symptom, having occurred in 95 per cent of this series, frequently with vomiting. In some there was an apoplectiform onset while headache, vomiting, papilledema, marked changes in motor power and reflexes, drowsiness or stupor, rigidity of the neck and a Kernig sign were noted as the principal prodromal signs and symptoms of the ensuing illness. The tumors were usually large spongioblastomas of various types, three being combined with tuberous sclerosis, and were most often located in or near the temporal lobe. The differential diagnosis from acute encephalitis or a vascular lesion was often difficult at first, but the degree of papilledema and the progress of symptoms were more often those of an intracranial expanding lesion. Treatment, surgical or otherwise, gave equally poor results, but life was most prolonged by partial or complete removal of the tumor. Craniotomy was

3. Wilson, G., and Winkelman, N. W.: Atlantic M. J. **28**:285 (Feb.) 1925.

4. Elsberg, C. A., and Globus, J. H.: Tumors of Brain with Acute Onset and Rapidly Progressive Course, Arch. Neurol. & Psychiat. **21**:1044 (May) 1929.

performed in twenty-two cases, with a defect left in the dura and bone for decompressive purposes. Six patients lived for from one to three months after the operation; one recovered and is well after two years. The average duration of life after admission to the hospital was thirty-four days, and the total average illness from the onset of the first symptoms was seventy-six days. Eighty-six per cent of these tumors were located above the tentorium and 14 per cent in the posterior cranial fossa; 81 per cent were spongioblastomas and one-sixth were of benign gliogenous growth histologically. The gliomas were located in the cerebellum or pons with one exception. Four cases showed multiple growths. Hemorrhage into the tumor occurred in several and extensive softening in two.

SUMMARY AND CONCLUSION

In the sixty cases reviewed and the ten here reported, the average age was 45 years. Forty-six of the patients were males and twenty-four females. The entire duration of illness averaged fifty-eight days, varying from seven days to four months, except in nine patients who lived from five to ten months after the initial symptom of trouble and one who was well after two years. This short duration of illness contrasts markedly with the average duration of life in cases of brain tumor. The exact duration cannot be stated definitely, but depends on the location and type of the tumor.

The tumors in the thirty-three cases here reviewed were located in the frontal region in seventeen, the frontoparietal in two, the temporal lobe in four, the occipitoparietal region in three, the basal ganglion in two, both pontocerebellar angles in one and the cord in one—an incidence of 91 per cent supratentorially and 19 per cent subtentorially, which agrees closely with the location of those reported by Elsberg and Globus, especially in relation to the tentorium.

Microscopically, exactly 90 per cent were spongioblastoma multiforme—one of these here reported was a medulloblastoma, and six included in the series of Elsberg and Globus were reported to be of gliogenous growth.

Many of the cases presented unusual clinical pictures with the acute onset, rapid progress and early fatal termination, the atypical features shown often simulating either inflammatory or vascular brain disease, making diagnosis very difficult and at times impossible.

THE DISTRIBUTION OF METASTATIC TUMORS IN THE CEREBRUM *

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The locations at which metastatic tumors of the brain most frequently occur have been the subject of little attention on the part of pathologists and neurologists. A considerable number of writers on the pathology of the nervous system and on the subject of tumors of the brain fail to consider metastatic tumors, while others who mention the existence of such neoplasms in the central nervous system do not discuss their distribution in the cerebrum.

Metastatic new growths in the encephalon may be single,[1] or there may be from two to five nodules.[2] In these instances the tumors are usually large when the brain is examined at necropsy or exploratory operation. Even when the exact location is given in the description, it is not possible to locate accurately the point at which the growth started. In general, both the cortical and the deeper regions of the cerebrum are involved. Five investigators[3] reported multiple metastatic nodules

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1. Arena, G.: Intracranial Lymphosarcosis: From Aleukemic Lymphadenosis? Riforma med. **42**:745, 1926. Brouardel; Renard, and Lotte: Metastatic Tumor of the Brain Secondary to a Primary Cancer of the Lung in a Syphilitic Subject, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:427, 1926. Clark, W. A.: Sarcoma of Brain with Secondary Actinomycosis Simulating Encephalitis, J. Missouri M. A. **18**:321, 1921. Weiman, W.: Ueber melanotischen Geschwülste in Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **85**:508, 1925.

2. Babinski, J.; Jarkowski, J., and Bethous: Sarcome mélanique du cerveau à foyers multiples, Rev. neurol. **38**:331, 1922. Duret, H.: Les tumeurs de l'encéphale, Paris, Félix Alcan, 1905. Meyer, E.: Zur Kenntnis der Carcinomatosen des Zentralnervensystems, Arch. f. Psychiat. **66**:283, 1922. Toulouse, E.; Marchand, L., and Pezé: Troubles mentaux symtomatiques des métastases cancéreuses encéphaliques, Encéphale **19**:414, 1924.

3. Buchholtz: Casuistischer Beitrag zur Kenntnis der Carcinome des Zentralnervensystems, Monatschr. f. Psychiat. u. Neurol. **4**:183, 1898. McKendree, C. A., and Feinier, L.: Somnolence: Its Occurrence and Significance in Central Neoplasms, Arch. Neurol. & Psychiat. **17**:44 (Jan.) 1927. Morse, M. E.: Two Cases Illustrating the Pathologic and Psychiatric Aspects of the Carcinomatous Metastasis of the Central Nervous System, J. Nerv. & Ment. Dis. **58**:409, 1923. Parker, L. H.: Involvement of Central Nervous System Secondary to Primary Carcinoma of Lung, Arch. Neurol. & Psychiat. **17**:198 (Feb.) 1927. Weston, J. G.: Two Cases of Secondary Sarcomatous Deposits in Cerebrum, Guy's Hosp. Rep. **76**:185, 1927.

which have a generalized, deep, as well as a superficial, distribution in the cerebrum, and there is one description [4] of tubercles confined to the cerebellum and pons. In a number of brains which have been described,[5] the metastatic nodules were confined to the meninges and involved the substance of the brain only by direct invasion.

Auvray [6] stated that tubercles may form in the brain following tuberculosis elsewhere in the body. They occur anywhere in the cerebrum, but with predilection for the most vascular regions. They may also occur in the cerebellum, but are rarely found in the basal ganglia. They are frequently multiple. He gave a sketch of a horizontal section through a cerebral hemisphere to illustrate the dissemination of tuberculous lesions in different parts of the cortex and white matter, which shows three nodules in the white matter within a short distance of the cortex. Henschen [7] described a brain that contained five metastatic melanosarcomas. He printed a picture of a frontal section through one hemisphere which shows four nodules that are either in the cortex or in the immediately subcortical white matter. Globus and Selinsky [8] reported a necropsy in which a brain was found that contained four sarcomas in the cortex of the cerebrum and one in the cerebellum. Seifert [9] described a brain, the cerebrum of which contained two large carcinomas and about fifteen small ones at the junction of the white and gray matter. Locke [10] stated that he found most metastatic carcinomas in the paracentral and pituitary regions of the brain. He believed, however, that this is only because tumors in these regions cause symptoms which call for examination of the brain at necropsy.

Gallavardin and Varay [11] described a brain which contained between 150 and 200 small secondary carcinomatous nodules, all in the gray substance of the cortex, one large nodule in the cerebellum and two small nodules in the basal ganglia. They reported more than three

4. Fumarola, G.: Multiple Cerebral Tubercles; Clinical and Anatomicopathologic Contribution, Arch. Neurol. & Psychiat. **7**:153 (Feb.) 1922.

5. Guillain, G., and Darquier, J.: Sarcome mélanique à foyers multiples, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1788, 1927. Meyer (footnote 2, third reference). Moorhead, G., and Wigham, G.: Meningitis Carcinomatosa: Report of a Case, Irish J. M. Sc., March, 1926, p. 135. Morse (footnote 3, third reference).

6. Auvray, M.: Les tumeurs cérébrales, Paris, J. B. Baillière et fils, 1896.

7. Henschen, S. E.: Klinische und anatomische Beiträge des Gehirns, part 1, Uppsala, Almqvist & Wiksells, 1890.

8. Globus, J. H., and Selinsky, H.: Metastatic Tumors of the Brain, Arch. Neurol. & Psychiat. **17**:481 (April) 1927.

9. Seifert, E.: Ueber multiple Carcinomatose des Zentralnervensystems, Arch. f. Psychiat. **36**:720, 1903.

10. Locke, C. E.: Les tumeurs du cerveau, Paris, Louis Arnette, 1922.

11. Gallavardin, A., and Varay, F.: Étude sur le cancer sécondaire du cerveau, du cervelet et de la moelle, Rev. de méd. **23**:441 and 561, 1903.

nodules in ten of fifty necropsies in which metastatic tumors of the cerebrum were found. They also considered the distribution of the tumors. At the level of the cerebrum, cancerous nodules seem to be situated with equal frequency in all lobes; tumors of the rolandic and superior parietal regions are especially common. These metastatic nodules ordinarily have a cortical or subcortical position and are rarely central. Some of them, often voluminous, affect the meninges and extend into the gray matter of the cortex. The cortical or subcortical predominance of the sites of the tumors is, according to these writers, due to the richness and fineness of the vascular plexus of the convolutions, which acts as a filter for the cancerous emboli which pass through the plexus of the pia. The basal ganglia may also be the site of metastatic nodules, but they rarely develop in the central white matter because the cellular emboli are always stopped at the level of the convolutions.

REPORT OF CASE

The brain to be described illustrates the tendency of metastatic tumors to form in the cortical or immediately subcortical regions.

The brain was taken from a white man, who died at Cook County Hospital on Jan. 20, 1927, at the age of 54, following an illness that had lasted for about forty days. The earliest symptoms were headache, vertigo and nocturia, to which were later added physical signs in the chest, poor ocular coordination, general ataxia with a tendency to fall to the left, drowsiness, loss of pupillary and corneal reflexes, rapidly developing blindness and coma, which alternated with restlessness until death.

Necropsy revealed a primary lymphosarcoma of a left pulmonary hilum lymph node, with metastases to the brain, both suprarenals, right kidney, mediastinal lymph nodes and pancreas; tumor thrombosis of the left lateral dural sinus; hyperemia and edema of the leptomeninges and brain.

The brain, hardened in formaldehyde, including the cerebrum, cerebellum, midbrain, pons and medulla, weighed 1,029 Gm. and was symmetrical, except for marked postmortem flattening. The blood vessels of both the brain substance and the leptomeninges were prominent and distended with blood. The only abnormality visible on the exterior of the brain was an irregular opening in the left occipital lobe where the largest of the tumor nodules reached the surface and where the necrotic material in its center had been displaced, probably by postmortem handling.

The brain contained twenty-three nodules. A typical nodule consisted of a firm white homogeneous center, occupying from one half to one third of the nodule, which was surrounded by a light gray, soft, granular material that extended to the smooth surface of the adjacent normal tissue. Microscopic sections from the nodule in the cerebellum showed it to be a lymphosarcoma with a necrotic center. There was one small nodule in the left side of the pons at the level of the facial colliculus, and a larger one occupied the greater part of the right lobe of the cerebellum.

The remaining twenty-one nodules were in the cerebrum. For descriptive purposes they fall readily into two groups, one cortical and the other subcortical. The cortical group consisted of twelve tumor masses which varied from 2 to 11 mm. in size and were usually spherical, but were sometimes spindle shaped. In every

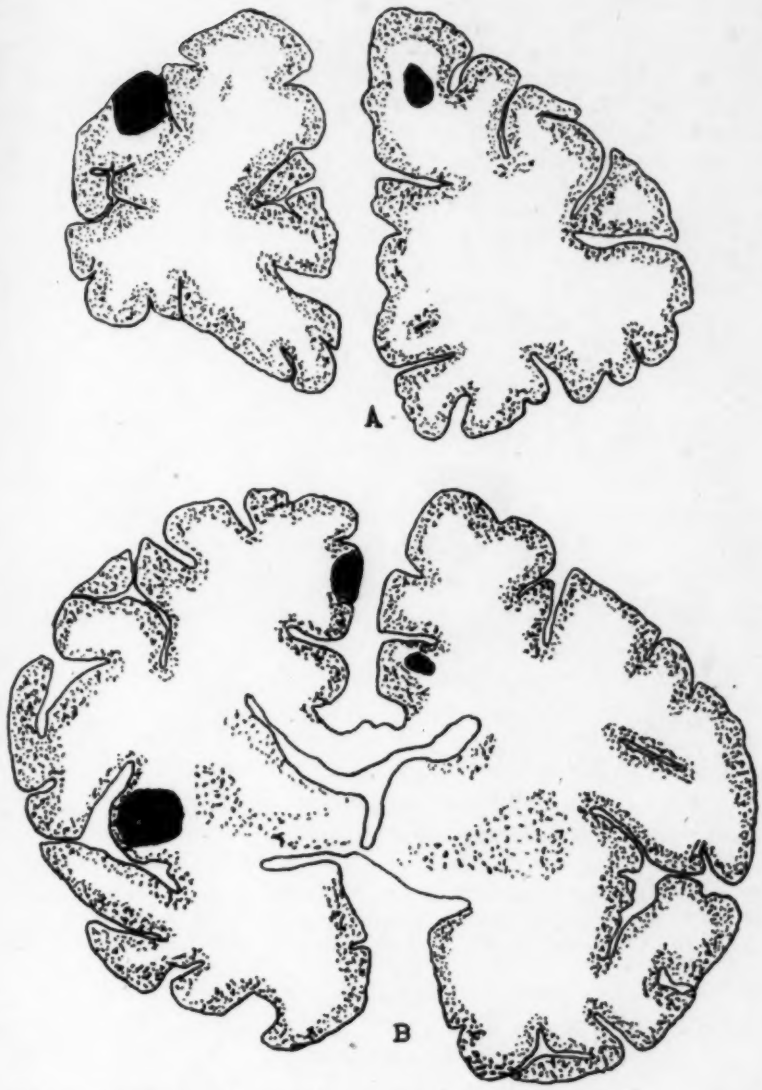

Fig. 1.—Frontal section through the cerebrum; *A*, the frontal lobes; *B*, the level of the mammillary bodies; showing the locations of two cortical and three subcortical nodules.

instance the main mass of the nodule was located in the gray matter of the cortex, as was also its center, but eight of the tumors extended slightly into the subjacent white matter. Four of the superficial masses were in the right frontal lobe, two in the left frontal lobe, three in the right parietal lobe and one each in the left parietal and right and left temporal lobes.

The subcortical group consisted of nine nodules which were located mainly in the immediately subcortical white matter, but never more than 4 mm. below the surface of the brain. They varied from 5 to 23 mm. in size and were most frequently spherical, but were occasionally spindle shaped or irregular, following the contour of the overlying cortex. The center of the tumor was in every case subcortical, but four of the nodules extended into the gray matter and one reached the surface in the left occipital lobe, as already described. Three of these deep masses were located in the left parietal lobe, two in the left occipital lobe and one

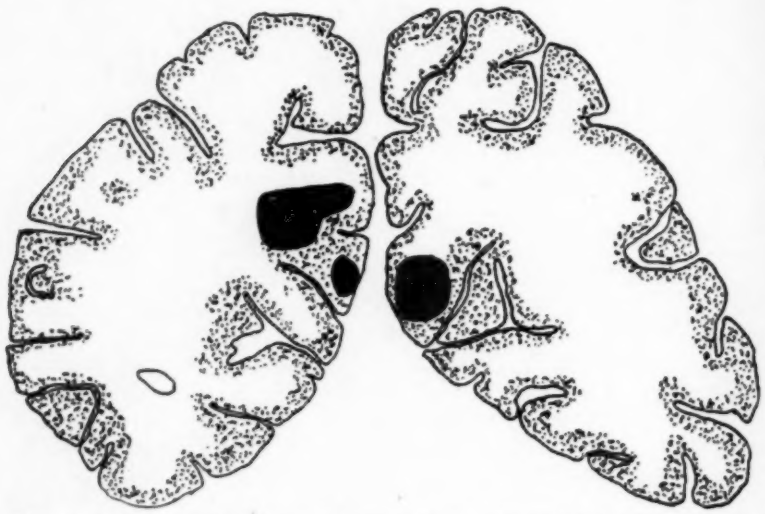

Fig. 2.—Frontal section through the cerebrum, the occipital lobes, showing the locations of one cortical and two subcortical nodules.

each in the right and left frontal and right parietal lobes and beneath the right insula. The accompanying sketches (figs. 1 and 2) of frontal sections through the cerebrum show the locations of three cortical and five subcortical nodules.

COMMENT

The distribution of metastatic tumors which has just been described appears from the literature to be the most common type in cases of multiple metastases. In considering the mechanism by means of which the metastatic nodules came to be located in this distribution, it may be assumed that the dissemination of the neoplastic cells was hematogenous. This assumption is justified by several considerations. The neoplasm was a sarcoma, the usual route of spread of which is the blood stream. The presence of a tumor thrombosis in one of the sinuses indicates that the sarcoma cells were actually circulating in the blood. Finally, the

brain was not connected with the general lymphatic system of the body, precluding spread by that channel.

Three factors must be taken into account in order to understand the locations at which hematogenous metastases arise. One is the vascularity of the region. Other things being equal, neoplastic emboli are most likely to reach the parts of the brain which have the greatest blood supply, since the greater the amount of blood reaching a given area the greater will be the number of particles brought by it to that area. Second, and more important, is the fineness of the vascular network. The sarcoma or carcinoma cells are very small, much smaller than an embolus resulting from a loosened thrombus or endocardial vegetation, and they must be stopped by very fine arterioles or capillaries in order to set up metastases. Finally, the neoplastic embolus must lodge in a tissue that is well supplied with blood vessels or else the anemia resulting from the plugging of a single vessel will deprive the tumor cells of the nourishment necessary for their growth and multiplication, and they will die.

If the blood supply of the convolutions is examined, it will be found that the arterioles derived from the cerebral arteries form loops in the pia mater. Two sets of vessels spring from these loops and penetrate directly into the subjacent convolutions. One set, the short arterioles, enters the cortex and immediately gives rise to a rich capillary plexus in the substance of the gray matter. The long arterioles, on the other hand, pass through the cortex and enter the medullary substance for a few centimeters, where they also give rise to a capillary plexus. In both instances the vessels are terminal arteries, and the capillary plexus is confined to the territory of the arteriole from which it arises and does not connect with the adjacent capillary plexus.[12] It is obvious that the two sets of metastatic tumors in the brain described, the cortical and the subcortical, occur, respectively, in the capillary plexuses at the ends of the short and long arterioles of the convolutions.

These two sets of capillary plexuses present precisely the three conditions which were mentioned as favoring the start of hematogenous metastases. The convolutions are highly vascular, and the large amount of blood passing through the vessels which supply them offers a good probability of tumor cells reaching them. It must be remembered further that the cortex is spread out over the entire cerebrum and thus occupies a greater area and receives a greater amount of blood than does the region of the basal ganglia. This condition alone would account for the more frequent location of metastases in the convolutions than in the basal ganglia.

12. Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, New York, Paul B. Hoeber, 1923, p. 724.

The second factor favoring lodgment of an embolus is the presence of fine capillaries. These are to be found in all parts of the brain. That they occur elsewhere than in the convolutions is testified to by the frequent occurrence of embolism in the basal arteries. The latter, because of their location close to the ends of the internal carotids, provide a relatively straight path for embolic particles to sweep up into the substance of the brain. Yet metastatic tumors do not occur most frequently in the parts of the brain supplied by them. It is therefore necessary to seek further for the condition which results in metastases occurring most often in the convolutions while other emboli seem to lodge most frequently in the basal parts of the cerebral hemispheres.

A solution to this problem is to be found in the type of capillary plexus which occurs in the cortex and the subcortical white matter. Terminal arteries are the rule in the brain. When there is no anastomosis, a tumor cell may lodge in a capillary, but it will die from lack of blood supply once it has plugged the capillary. It seems highly probable that many such emboli do actually settle in the capillaries of the basal ganglia. A few live, resulting in the occasional occurrence of metastases in these regions which are reported in the literature. But the majority die from lack of nourishment, with the result that metastatic tumors in the basal regions are less frequent than in the convolutions. Nor do the other symptoms of embolism usually appear in such instances, since the emboli are so small that only a single capillary is plugged and the resulting ischemia occurs in so minute an area as to be unnoticed both functionally and at necropsy.

In the convolutions, while each arteriole is a terminal artery that does not anastomose with its neighbor, the arterioles do break up into capillary plexuses where there are interconnections. A tumor cell is so small that it passes through the arteriole and is not stopped until the capillaries are reached. One capillary is plugged by the embolus, but the surrounding network still supplies the blood. The neoplastic cells have nourishment and grow to form a metastatic nodule. This may occur either in the plexuses of the cortex or in those in the subcortical white matter of the convolutions, with the result that metastatic tumors are frequent in both locations, as has already been shown.

Yet embolism of other types appears to be comparatively rare in the cortical and subcortical areas. There is no *a priori* reason why other particles of solid material in the blood should not find their way here as readily as do tumor cells. If they do so, an anemic area will result from the plugging of an arteriole or capillary. It seems likely that many of these emboli not only occur in the convolutions but pass unnoticed, often without symptoms that call for examination of the brain at necropsy. The reason for this is to be found in the relative diffuseness of cortical function. The very fine localization that occurs

in the internal capsule, on the other hand, will cause marked symptoms from an anemic area of such size as to pass unnoticed clinically when it occurs in the cortex. This is illustrated in the brain which has been described. Although there are twenty-one lesions in the convolutions, only the largest one, which was located in the occipital pole and was over 20 mm. in length, gave definite symptoms that were sufficiently prominent to appear on the hospital record. Aside from the visual disturbances due to it and the ataxia due to a tumor in the cerebellum, which was almost as large, there are only the general symptoms resulting from increased intracranial pressure.

One may conclude, then, that the vascular supply of the brain is such that the cerebral cortex and the immediately subcortical white matter offer the best conditions for the lodgment and growth of metastatic tumors.

HEPATOLENTICULAR DEGENERATION

A REPORT OF THREE UNUSUAL CASES *

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The concept of progressive lenticular degeneration as a clinicopathologic entity has changed since its first delineation by Wilson [1] in 1912. Characterized clinically by progressive symptoms referable to the basal ganglia, often clearly familial in incidence, usually occurring in young persons, running either an acute or a chronic course and always fatal, at autopsy every case has shown nodular hypertrophic cirrhosis of the liver, as well as degeneration of the putamen and caudate nuclei. The nervous lesions are sometimes more widespread, with cortical and cerebellar involvement. Through the work of many others, but notably Hall,[2] there has developed a more liberal concept which includes Wilson's disease with the pseudosclerosis of Fleischer under the general term "hepatolenticular degeneration." Although there are points of difference between the two diseases that merit attention, still the nomenclature has been generally accepted and has been vigorously upheld by recent English writers.

One of the most interesting clinical features of the disease is the frequent occurrence of a peculiar greenish-brown pigmentation of Descemet's membrane near the limbus. This was first noted by Fleischer in two cases of pseudosclerosis with cirrhosis of the liver. According to Hall, the characteristic corneal pigmentation was found in all sixteen cases of pseudosclerosis reported, and in four of nine cases of Wilson's disease. Since then, Greenfield, Poynton and Walshe [3] have added one, and Barnes and Hurst [4] two to the list of Wilson's disease with such

* Submitted for publication, Sept. 20, 1929.

1. Wilson, S. A. K.: Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver, Brain **34**:295 (March) 1912.

2. Hall, H. C.: La dégénérescence hepatolenticulaire, Paris, Masson & Cie, 1921.

3. Greenfield, J. G.; Poynton, F. J., and Walshe, F. M. R.: On Progressive Lenticular Degeneration: "Hepato-Lenticular Degeneration," Quart. J. Med. **17**:385, 1924.

4. Barnes, Stanley; and Hurst, E. W.: Hepato-Lenticular Degeneration, Brain **48**:279 (Sept.) 1925; A Further Note on Hepato-Lenticular Degeneration, ibid. **49**:36 (March) 1926; Hepato-Lenticular Degeneration: A Final Note, ibid. **52**:1 (April) 1929.

pigmentation. It is significant that this so-called Kayser-Fleischer zone is always associated with the characteristic cirrhosis of the liver, and according to Barnes and Hurst, only three cases in which the zone of pigment was found without neurologic evidence of Wilson's disease or of pseudosclerosis are recorded. Of these three cases, two occurred in families other members of which suffered from typical Wilson's disease or pseudosclerosis. The third case, Kraupa's,[5] occurred in a boy, aged 14, without nervous signs and without recorded familial history of hepatolenticular degeneration. In this case, the liver edge was hard and extended two finger-breadths below the costal margin, but liver function was normal. Both eyes showed the typical Kayser-Fleischer zone. The boy suffered from congenital syphilis and had had syphilitic retinochoroiditis. He had been jaundiced for two years. Kraupa stated that the pigmentation was in all probability the result of the liver disease.

The finding of the Kayser-Fleischer zone in a case of juvenile cirrhosis is considered evidence sufficient for the diagnosis of hepatolenticular degeneration, even without signs referable to the central nervous system, for if one accepts the toxic origin of the disease the liver and eye signs may conceivably develop before the nervous signs.

The present study deals with a family in which three members suffered from cirrhosis of the liver; two died of the disease and the third, still living and unaware of his true state, shows a hugely hypertrophied liver, deficient liver function and a typical Kayser-Fleischer zone. These three patients have shown nervous signs of no intensity, when present at all, their troubles being largely mental.

The first case was observed by us first at the American Hospital of Paris, later by one of us at the Henry Phipps Psychiatric Clinic of the Johns Hopkins Hospital, and will be discussed first as showing the minimal requirements for inclusion in the hepatolenticular group.

REPORT OF CASES

CASE 1.—F. B., a man, aged 32, came to the outpatient department of the American Hospital of Paris on June 13, 1929, with the complaint of inability to play the violin, and of being depressed.

Family History.—The patient was one of a family of five children of Russian Jewish parentage. The father was a band leader in the Imperial Grenadier Guards in Russia. In 1905, he, with the patient's older brother, witnessed a pogrom. He became so nervous after this that he left Russia and came to America. He died at 55 years of age of "multiple sclerosis," according to the statement of another brother, a physician. Nothing is known of his forebears. The mother was living, aged 60, and suffered from high blood pressure. Her family was said to have been healthy and long lived.

5. Kraupa: Zu Fleischers grünlicher Hornhautverfärbung, Klin. Monatsbl. f. Augenh. **69**:526, 1922.

Three members of the patient's immediate family were living:

1. A sister, aged 38, a musician, who was said to be nervous. She had no corneal pigmentation.

2. The patient, aged 32.

3. A brother, aged 30, a physician, in good health, and characterized by the patient as different entirely in personality from himself. He had no corneal pigmentation.

Two members of the family were dead:

1. A brother (the patient in case 2), the eldest of the family, died in 1928, at the age of 38, of cirrhosis of the liver and about eight tappings for ascites. He was a talented musician. His personality is said to have been much like that of the patient. He had some subcutaneous nodules on the arms before death. His illness lasted about nine months. There was a questionable history of alcoholism.

2. A sister (the patient in case 3), the youngest of the family, died in 1925, at the age of 22, of cirrhosis of the liver with intense jaundice and ascites. She was tapped about eight times, and her illness was of about seven months' duration. There was no history of alcoholism. She was a musician, was married a year before death, and unhappily. There were no children.

Personal History.—The patient came to America at the age of 8. He was always well. He had scarlet fever as a child and possibly influenza, but no typhoid fever. The history otherwise was unimportant. The patient was always morose, cynical, depressed and unsociable. He was irritable and stuttered often. He did not change after marriage six years ago. There were several separations because of a clash of temperaments. He threatened suicide several times. He was depressed because of this domestic incompatibility.

The patient became gradually more depressed following the death of his sister in 1925 and of his brother in August, 1928. In addition, he noticed on himself the same kind of subcutaneous nodules that his brother had before death. According to his wife, he cried easily and laughed "hysterically." About eight months before examination, he noticed that his right arm trembled so much as to interfere with playing the violin in the New York Symphony Orchestra. Shortly afterward, he noticed that the fingers of the left hand were stiff; when they assumed the position for fingering, they trembled. Six months before examination, he was forced to cancel his contract with the orchestra. He then came to France for a change of environment. After quitting work, he did not touch the violin and did not want to try to play, but could use his hands perfectly for buttoning his clothes and other fine movements. The right arm shook, and he dropped things often. There was no shaking when the arm was at rest; he wrote well, slept poorly and took no exercise. Occasionally, he felt a sharp pain in the region of the fifth rib on the right in the midclavicular line; this became more frequent. The bowels moved regularly; there was no nausea, vomiting or jaundice; appetite was poor. He weighed 145 pounds (66 Kg.), a loss of 20 pounds (9 Kg.) from his best weight during the World War. Recently, he had had bleeding hemorrhoids, but these were causing no trouble.

Examination.—The patient was well developed and nourished; his hair was unusually gray for his age; there was a café-au-lait coloration of the skin; he wore glasses. There was a rather sad expression to the face; the patient talked slowly, distinctly and without defect. The sensorium was normal. There was no emotional overaction, with laughing or crying spells.

The eyes were myopic; the pupils were equal, regular and central, and reacted actively to light and in accommodation. There was a band of brownish pigmentation about the edges of the cornea, 1 mm. wide. In ophthalmoscopic examination, the disks were well outlined; the vessels were normal; there was no exudate or hemorrhage. The media were clear; visual acuity and fields were normal.

The tongue was coated. The thyroid gland was normal. The lungs were normal. The heart was normal; the blood pressure was 130 systolic and 75 diastolic.

The abdomen protruded slightly, but definitely, in the right upper quadrant, and was dull to percussion and firm to palpation. The mass moved downward on inspiration. The edge of the mass, evidently the liver, was felt on a level with the umbilicus on inspiration, was rounded, was not tender and was regular. The abdomen elsewhere was soft and tympanitic.

The skin showed numerous hemangiomas over the trunk; there were several small subcutaneous nodules on the arms, which were apparently lipomas.

The genitalia were normal. The anus showed one hemorrhoidal tag.

When the arms were held outstretched, there was a coarse tremor of the right, and it soon drooped. The grips were strong. There were no involuntary movements when the arms were at rest. There was slight unsteadiness with the right arm when reaching for a glass of water, and bilaterally when attempting the finger-to-nose test. Slight dysdiadokokinesia was observed with the right arm. The patient did not drop objects held in either hand.

Course.—On June 18, the patient felt much cheered. The tremor of the hand was gone, and the right arm no longer drooped when held outstretched.

On June 20, a slit-lamp examination by Dr. Edouard Hartmann showed the pigmentation to be a beautiful golden bronze on the posterior surface of the cornea near the limbus; it was sharply demarcated medially. Dr. Hartmann reported that this band was absolutely typical of that seen in Wilson's disease. In addition, he noted that the fundus, pupils and fields were normal; vision was from 8/10 to 9/10 (myopia); slight nystagmus was observed when looking either to the right or to the left.

The patient was more cheerful on this day. He called attention to the tremor of the fingers of the left hand, when they assumed the position they would take in playing the violin. There was also a fine tremor of the extended fingers. Meyer and Hoffman reflexes were absent. The deep reflexes were all present, active and equal on the two sides. Babinski's sign was absent.

On June 27, Dr. Lhermitte noted: no atrophy; slight hypotonia of the left upper extremity on passive movement of the forearm and hand; Gordon Holmes' sign absent; no dysdiadokokinesia; slight unsteadiness in the finger-to-finger test when attempted from the oblique positions, less so from the horizontal; tongue normal, and gait normal. Station showed slight weakness on the left, the patient being less able to support himself on the left leg than on the right. Formerly, he walked long distances; he tired easily now. All tendon reflexes were present and active. The superficial abdominal reflexes were present. Associated movements of the thumbs on hyperextension of the fingers were normal. No tremor or weakness was noted in the extended arms or hands. There was a suggestion of catatonia when the arms were placed in awkward positions. There was a well marked dermographia following scratching with a pin, a white wheal along the scratch mark surrounded by a zone of erythema soon developing.

The spleen was definitely enlarged and was felt as a long, narrow, firm mass extending obliquely almost to the umbilicus.

The patient stated at this time that four months before he could put a pin into his finger without pain, and that his mental condition became so serious that it was feared he would have to be placed in a psychopathic hospital. He reported improvement at the time of examination, but said that he could not play the violin, the clumsiness and unsteadiness in the fingers reappearing.

Laboratory examinations made at this time showed:

Wassermann Test of the Blood: Fresh serum negative; heated serum negative.

Urine: Sugar present; urobilin present.

Blood: Hemoglobin, from 70 to 75 per cent; red cells, 4,280,000; no anisocytosis or poikilocytosis; no young red cells.

Blood Chemistry: Urea, 40 mg.; sugar, 104 mg., and cholesterol, 215 mg. per cent.

Van den Bergh Test: Direct, delayed, slightly positive results.

Rose Bengal Test of Liver Function: Less than 3 mg. per liter of the dye present after forty-five minutes (normal).

Further Examination.—In October, 1929, the patient was admitted to the Johns Hopkins Hospital for further study by one of us. During the interval since early in July, 1929, the mental symptoms had not changed. The same neurologic signs were present. At this time, the spleen was huge, reaching one finger-breadth below the umbilicus, and completely filling the left upper quadrant. It was hard and notched. The liver was felt at the level of the umbilicus on deep inspiration, and was hard and smooth. Dilated venules were prominent along the lower costal margin, and there was a puffiness with a brown splotchy pigmentation over the ankles. Marked hyperhidrosis of the hands was noted at this time, and the patient said that it had been present for about a year.

Laboratory examinations made at this time showed:

Blood: Hemoglobin, 80 per cent; red cells, 4,350,000; no anisocytosis or poikilocytosis; no color changes or young cells; white cells, 6,200; polymorphonuclear cells, 62; lymphocytes, 26; mononuclear cells, 7, and polymorphonuclear eosinophil cells, 2.

Blood Chemistry: Urea, 48.4 mg.; sugar, 98 mg.; cholesterol, 203 mg. per cent; sugar tolerance: fasting specimen, 79.4 mg.; one hour after ingestion of 50 Gm. of dextrose, 160 mg.; two hours after, 95 mg. per cent.

Fragility Test: Initial hemolysis began at 0.44 per cent, and hemolysis was complete at 0.28 per cent—a widening of the normal zone in either direction.

Sedimentation Time: First hour, from 100 mm. to 91 mm.; second hour, to 78 mm. (normal).

Urine: Sugar, none; diacetic acid, present; hyaline casts.

Macroscopic Examination of Blood: No Oppler-Boas bacilli or sarcinae.

Gastric Analyses (Fasting Specimens): (1) p_H greater than 7.9; free hydrochloride none, total hydrochloride none, lactic acid present; (2) no free or combined hydrochloric or lactic acid present; (3) specimen taken forty minutes after the subcutaneous injection of 1 mg. of histamine, p_H 7.4, free hydrochloric acid none, total hydrochloric acid 5 per cent, lactic acid none. It was impossible to take fractional specimens because of the active vomiting reflex.

Summary.—A man, a Russian Jew, aged 32, depressed over the untimely death of a sister and a brother of cirrhosis of the liver, found on himself some stigmas resembling those of the brother who died. In addition, he developed (November, 1928) unsteadiness in the hands, so that he had to stop work as a violinist. The depression deepened. In

June, 1929, he showed conflicting neurologic signs which depended apparently on his mood, which was labile; there was probably a real nystagmus, slight incoordination of the upper extremities, hypotonia of the left arm and weakness of the left leg. In addition, there were well marked dermographia, enlarged spleen and liver, deficient liver function and the typical Kayser-Fleischer zone in both corneas. In October, 1929, he showed progression of the condition with early signs of portal obstruction. In addition, there was noted a marked hyperhidrosis of the hands and coarse tremors of the hands, which came and went and were not always elicitable. At this time, he was noted to have complete absence of hydrochloric acid, both free and combined, and little combined acid even after the injection of histamine.

The mental symptoms far outweighed the neurologic; at times, the latter could be easily overlooked.

The second patient was observed by Dr. Lewellys F. Barker, of Baltimore, through whose kindness we are able to include this report:

CASE 2.—*Clinical History.*—A. B., a man, aged 38, was seen by Dr. Barker on April 18, 1928, because of swelling of the ankles and ascites. The family history has already been outlined. The patient was always nervous, owing, he thought, to his work. He was a violinist for the New York Symphony Orchestra. He had some hyperhidrosis, which was treated by the roentgen rays. There was some history of alcoholism, but he had had none for the past two months.

He had had edema of the ankles for the past five months and ascites for two months. On March 1, the icterus index was 28.5, later dropping to 18. Paracentesis was performed ten days before examination with the removal of 4½ quarts of ascitic fluid. At this time, the liver and the spleen were both palpable and slightly enlarged.

Examination.—There was a brown tinge to the skin. The conjunctivae showed a faint suggestion of icterus. There was beginning canities, with considerable calvities of the temples. Ophthalmoscopic examination of the eyes gave negative results. The pupils were normal; there were no signs of hyperthyroidism. A slight arcus senilis was present bilaterally. There was mild tremor of the extended tongue. The blood pressure was from 90 to 104 systolic and from 44 to 54 diastolic.

Abdominal ascites was present, and the liver probably was enlarged. The spleen was not felt.

The reflexes were present. There was no evidence of pyramidal disease.

Laboratory Examinations.—Dr. Rosenthal, of New York, reported: Bromsulphthalein Test: 35 per cent retention of the dye at the end of one hour; icterus index, 18.

Blood Count: normal. Fragility Test: hemolysis began at 48 and was complete at 36. This showed a widening of the range of hemolysis in both directions, that of greater and lesser dilutions. Coagulation time: 10 minutes. Bleeding time: 5 minutes. Sedimentation time: 5 hours.

Blood Chemistry: urea, 14.2 mg.; creatinine, 1.6 mg.; sodium chloride, 489 mg.; cholesterol, from 178 to 184 mg.

Van den Bergh Test: direct, positive; delayed, positive.

Urine: negative for albumin and sugar.

Stool: urobilin present, but much weaker than it is normally.

Basal Metabolic Rate: decreased 25 per cent from normal.

Phenolsulphonphthalein Test for Kidney Function: first specimen (1 hour), 65 per cent; second specimen (2 hours), 25 per cent.

Additional laboratory data secured from Dr. Barker were: Blood smear: slight anisocytosis and poikilocytosis; red cells slightly pale; no abnormal cells. Icterus index: 20 (the normal is about 6). Wassermann test of the blood: negative. Urine: sugar present; urobilinogen present; blood present; some white and red blood cells; hyaline casts. Roentgenogram of the sella: normal.

Diagnosis.—1. Ascites due to portal obstruction with hepatomegaly, and with a positive van den Bergh test in the blood, and urobilinogenuria. Probably chronic interstitial hepatitis, with a history of some alcoholism.

2. Secondary anemia; hemoglobin 75 per cent.

3. Slight nephropathy, with albuminuria and cylindruria.

4. Slight glycosuria.

5. Nervous constitution.

6. Slight undernutrition.

The patient's brother, a physician, stated that about six months before death there was noted, in an examination carried out at a small private sanitarium in New York, a marked hypo-acidity of the gastric contents.

The patient was not seen again by Dr. Barker. He was tapped repeatedly and died on Aug. 20, 1928.

Summary.—A man, aged 38, of nervous constitution, but well until five months before, was taken with edema of the ankles, and then, three months later, with ascites. A diagnosis was made of portal obstruction, with hepatomegaly and deficient liver function. Slight nephropathy and glycosuria were observed. The patient died four months after the diagnosis was made, and after repeated paracenteses. The Kayser-Fleischer zone was not noted; only an early arcus senilis was observed. Six months before death there was marked hypo-acidity of the gastric contents.

Information concerning case 3 came mainly from the brother, the physician; some minor points were learned from other members of the family.

Case 3.—This patient, a sister of the other patients described, died in 1925 at the age of 22 of cirrhosis of the liver with ascites and intense jaundice, and after several paracenteses. The first symptom was jaundice; then ascites appeared. Carcinoma was suspected and a laparotomy was performed; "the typical mottled appearance of the enlarged liver, and the enlarged red spleen (almost Banti's)" were found. The patient died in shock following a second operation at which an omentopexy was attempted. The time from the first symptom to death was only seven months. There were no neurologic signs or corneal pigmentation. Biopsy showed nodular cirrhosis of the liver and interstitial thickening of the spleen.

The patient had been married for a year before death, and was unhappy. There were no children.

SUMMARY OF THE CLINICAL OBSERVATIONS

The familial character of the disease of the liver here presented can scarcely be denied. Case 1 might be considered a sporadic case of hepatolenticular degeneration; case 2, chronic interstitial hepatitis, possibly on an alcoholic basis, although the evidence on this point is doubtful; case 3, in all respects like case 2, with added jaundice and without a history of alcoholism, makes certain the familial character of the malady. The incidence at ages 22, 32 and 38 bears out the essentially juvenile character of the disease. It is noteworthy that the patient now living considers his father and the brother and sister who died, and himself as much alike in personality, and in sharp contrast to the mother, and a brother and sister now living, whom he considers outgoing, materialistic and in no way like himself.

Liver.—Case 1 is notable for the large size of the liver, the absence of subjective liver disease and the paucity of objective signs. Most cases of hepatolenticular degeneration show little evidence of liver disease, the liver being rarely noted as large as in this case. It may be that in this case the liver will regress in size with an accentuation of the obstructive signs, which are already beginning to appear. Cases 2 and 3 were notable for the severity of the obstructive features. Case 1 is noted as showing a subicteric tint; case 2 as showing a faint suggestion of icterus of the conjunctivae, while in case 3 the patient is reported to have been deeply jaundiced.

There was laboratory evidence of deficient liver function in both cases 1 and 2: (1) urobilin or urobilinogen in the urine; (2) deficient coloration of the stool; (3) direct and delayed van den Bergh reaction positive; (4) icterus index 28.5 (case 2); (5) decreased elimination of the test dye (case 2); (6) sugar in the urine (perhaps a result of the nephropathy); (7) increased blood cholesterol.

Nervous System.—The signs of involvement of the central nervous system were minimal, if present at all. As noted in case 1, the clumsiness of the hands, tremors of the fingers and hands, slight hypotonia of the left upper extremity, weakness of the left leg, tendency to catatonia, slight incoordination of the upper extremities and nystagmoid movements were all insignificant beside the mental depression from which the patient suffered. The tremors of the hands actually disappeared as the mood became more cheerful. The moroseness, irritability and depression in case 1 were observed equally in cases 2 and 3. The three patients evidently had much in common in their personalities, abilities and inclinations.

Eyes.—Case 1 showed a typical Kayser-Fleischer zone of corneal pigmentation bilaterally. In case 2 there was an early arcus senilis.

In case 3 there was no corneal pigmentation. The brother and sister now living show no corneal pigmentation.

General.—Splenomegaly was noted in all three cases. Some evidence of nephropathy existed in cases 1 and 2, and was rather more marked in the latter. There was a moderate secondary anemia in both cases. The blood sugar was normal; urea was increased in case 2, and cholesterol was increased in both cases. Hyperhidrosis was noted in cases 1 and 2.

Gastric Contents.—There was complete absence of free and combined hydrochloric acid in the fasting contents of the stomach in case 1, and only an insignificant amount of combined acid was present after injection of histamine. In case 2 a marked hypo-acidity was noted. The physician-brother has an absence of free acid, and only 3 per cent of combined acid in the fasting contents. Case 1 was noted also as showing lactic acid in the gastric contents, but there was no other evidence of stasis.

DIAGNOSIS

We are dealing with a familial hepatic disorder of the nature of chronic interstitial hepatitis with deficient liver function. The series is notable because one case presents the typical Kayser-Fleischer zone of corneal pigmentation which makes the diagnosis of hepatolenticular degeneration probable. The general and detailed correspondence of the three cases would lead one to classify them all as the same disease, the absence of pigment notwithstanding. If this is granted, then the concept of hepatolenticular degeneration must be further altered.

In their illuminating report on a family of four persons with hepatolenticular degeneration, Barnes and Hurst concluded that the disease is due to a toxin elaborated probably in the alimentary tract which gives rise to successive attacks of interstitial hepatitis, and that the corneal and cerebral signs develop much later. In slowly progressive cases, the liver damage may not be clinically noticeable, the toxin by its selective action on the basal ganglia giving rise to nervous signs which completely dominate the picture. In more acute cases, the patient may die of liver disease with jaundice and ascites before nervous signs develop. However, in such an event, in the cases reported to date, there has always been present a Kayser-Fleischer zone. The presence of such a combination of signs in certain members of a family others of which suffered from typical Wilson's disease or from pseudosclerosis has been noted by Barnes and Hurst, von Dziembowski [6] and Jendralski.[7] Only Kraupa's case, developing after syphilitic retinochoroiditis

6. Von Dziembowski, S.: Zur Kenntnis der Pseudosklerose und der Wilsonschen Krankheit, Deutsche Ztschr. f. Nervenh. **57**:295, 1917.

7. Jendralski, F.: Der Fleischersche Ring bei Wilsonscher Krankheit. Klinischer und anatomischer Beitrag nebst Bemerkungen über den Hämosiderinring beim Keratokonus, Klin. Monatsbl. f. Augenh. **69**:750, 1922.

in a boy with congenital syphilis, showed no familial association with hepatolenticular degeneration. However, no one has ventured to include chronic interstitial hepatitis without the Kayser-Fleischer zone in the hepatolenticular group. If the unity of the three cases described here is granted, this further broadening of the concept must follow. May there not be cases in which the liver bears the brunt of the disease process to the clinical exclusion of both central nervous system and corneal signs?

The significant facts are that the liver damage is never absent in these cases, and that this damage is of a particular sort, leading to associated signs not seen in other types of cirrhosis.

ETIOLOGY

Without an anatomic report to accompany these cases, it is not our purpose to speculate on the etiology of this disease. However, it may not be amiss to digress for a moment and call attention to some theoretical considerations which would bear on the entire problem. The familial nature of the malady is certain. Aside from this, however, let us assume with Barnes and Hurst that there is a toxin which is elaborated in the intestinal tract and filtered through the liver before gaining access to the general circulation. The clinical and pathologic evidence of the disease appears in three regions: the liver, the brain and the cornea. Theoretically, the disease should be able to manifest itself in seven ways: (1) liver, brain and cornea; (2) liver and brain; (3) liver and cornea; (4) liver alone; (5) brain and cornea; (6) brain alone; (7) cornea alone.

Of these possibilities the first three have been often reported. The fourth possibility is presented here for the first time (cases 2 and 3) in familial association with a case (1) representing the third (or perhaps the first) possibility. Conceivably there may be many cases of chronic interstitial hepatitis of this special sort which are undiagnosed as such, because of the absence both of other incriminating evidence of the disease in themselves and of familial association with more outspoken examples of the disease. It is our judgment that cases 2 and 3 presented just such a situation.

The remaining three suggested manifestations, from what we know of the disease and in view of Barnes and Hurst's theory, are impossible, and it is significant that they have never been reported.

Barnes and Hurst have called attention to the advisability of making an analysis of the gastric contents in these cases on the possibility of finding hypo-acidity or anacidity, observations almost constant in subacute combined degeneration with or without the blood changes of pernicious anemia. In case 1 there was no hydrochloric acid whatever;

in case 2 a marked hypo-acidity, and one member of the family, living and well, has no free and little combined acid. This may be merely an interesting example of familial anacidity, but possibly has a real etiologic significance by letting down the barriers to the invasion of pathologic micro-organisms into the gastro-intestinal tract from the mouth. At most, these are the first cases to show such an association of observations, and the result of specific therapy in this direction will be awaited with interest.

CONCLUSIONS

1. Three cases of familial hypertrophic cirrhosis of the liver with splenomegaly, deficient liver function, and with absence of, or few, neurologic signs, are presented. Two patients have died after a short illness of the liver disease. The third is living and shows little evidence of deficient liver function.

2. The patient now living shows a typical Kayser-Fleischer zone. The diagnosis of hepatolenticular degeneration is therefore almost certain.

3. The three cases are presented as a family group showing hepatolenticular degeneration, the two patients who died as showing the special sort of liver damage of such a severity as to cause death before either cerebral or corneal signs could develop.

4. The etiologic significance of gastric anacidity in this family group may be important, and specific therapy in this direction is in progress.

5. Research into methods of identifying the toxic agent becomes important, so that differentiation between the special type of hepatitis involved and other types not having the same grave import may be made.

THE SENSE OF REALITY IN MENTAL DISEASE*

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It is the peculiar fate of methods advanced for the purpose of furthering progress in most fields of scientific endeavor to enjoy a life span that is in inverse proportion to their successful applicability. The more successful such a method is in solving problems and in opening up new fields for further research, and the broader the horizon that it opens up, the more likely it is to be overtaken by the very progress it has caused and thus to become inadequate. In the medical sciences, which have made such rapid progress within recent years, the condition has become particularly noticeable. New facts discovered bring up new problems, which call for a change of attitude and manner of attack. Methods only recently successfully applied must be discarded as they are rendered inadequate by the very discoveries they have helped to make. It is not always easy to rid oneself of a standardized manner of approach, however, and in some instances the old methods have become so deeply rooted that even the fact that they are inefficient, and at times directly reactionary, does not help in decreasing the influence exerted by them.

Such a state of affairs has become particularly evident recently in clinical psychiatry. I am referring to the systems of classification and description that were introduced into this branch of medicine toward the end of the last century. There is no doubt but that this method was of the greatest help in clearing up the confusion that had reigned for centuries in the study of mental diseases. It was this method in fact, more than any other, that helped finally to establish psychiatry among the medical sciences and clear the way for objective investigation. But the new fields that were thus opened have brought up altogether new problems for the solution of which new methods of approach have become imperative. There is no better proof of this than the fact that numerous attempts have been made within recent years to change the trend of thought in the study of mental diseases. In some instances, in fact, the desire to strike a new road seems to have been the sole impelling force in the establishment of superficially new and elaborate theories. These attempts, however, do not seem to have met with definite success. It would almost seem as if the dementia praecox-manic-depressive antithesis could not be dislodged from its corner-stone

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position in psychiatry. It is just as fundamental in Kretschmer's schizoid-cyclothymic characters as it is in Bleuler's dystonic-syntonic opposites and even in Jung's introvert-extrovert types. In clinical psychiatry proper, the substitution of "schizophrenia" and "affect disorders" for older names may have enriched, to a certain extent, the clinical understanding of such concepts, but has not succeeded in getting away from this method of approach.

A distinct advance from this point of view was made with the introduction of the dynamic approach; that is, the attempt to study mental disturbances on the basis of their evolution out of an interaction between special personality types and the situations in which the patients find themselves, rather than merely describing isolated stages in the clinical course. It soon became apparent, however, that the complete emancipation from the older methods could not be brought about by the introduction of dynamics alone. For here, too, one finds in many instances the studies of the evolution of psychoses built up around the previously established disease entities. One finds oneself, for instance, studying the evolution of schizophrenia with the schizophrenic end-product serving as the nucleus of the study. The same is true for a manic-depressive psychosis, and so on. The psychoanalytic school, which among others has played an important rôle in the introduction of dynamic studies, has from the beginning pointed out how important it is to disregard classifications not only in the field of the psychoses as such but in all mental disturbances, and that, in fact, for an understanding of such reactions it would even be important to break down the age old differentiations between so-called normal and abnormal behavior. Therefore, in a study of the mechanism of psychotic behavior, it will not be sufficient to study its evolution out of a certain prepsychotic type such as the schizoid type preceding the schizophrenic outbreak, but it will be necessary to establish the developmental relationship that exists between such a reaction and that of a normal person. It would seem that one logical way of approaching this problem would be to concern oneself with certain behavior anomalies rather than with disease entities. Behavior anomalies, furthermore, that are not particularly bound down to any single disease but in one degree or another may be found in all groups. An attempt should be made to understand these anomalies in terms of development out of given situations. As an example of this method of approach I shall present here the consideration of such a behavior anomaly.

The type of reaction that I shall discuss is one that is rarely found as the controlling feature of any type of mental disorder, but it is met with in different degrees of intensity at one stage or another in most, if not all, mental disturbances. This reaction can be best described under the term that most patients themselves apply to it, namely, that

of a sense of unreality. Most patients, when asked to describe it more fully, say that they have the feeling that some or all contents in their environment have changed; that they are not as they used to be, or as they are perceived by normal persons; they feel unreal. This change may effect certain objects or contents in the outside world or in the patient himself. It may affect everything, the outside world, different parts of the patient's body, and even his thoughts and imagery. A vivid description of such a state can be found in Schilder's "Outline of a Psychiatry on the Psychoanalytic Basis"[1] under the heading of depersonalization. This is one of the most pronounced forms of such a type of reaction: "The world appears strange, peculiar, foreign, dreamlike. The objects appear at times strangely diminished in size, at times flat. Sounds appear to come from a distance, the tactile characteristics of objects likewise seem strangely altered, and even their imagery appears altered . . . pale, colorless . . . The patients complain that they are capable of experiencing neither pain nor pleasure; love and hate have ceased within them . . . they have a feeling of being dead and lifeless like automatons."

REPORT OF CASES

CASE 1.—H. M., a single man, aged 24, was admitted to the hospital because of an acute excitement during which he became violent toward members of his family. To the physician who was called in to see him, he spoke of his discovery that he was "an artificial object, a product of a scientist. Everything outside was unreal. The white material on the street was not snow, etc." These statements were repeated by the patient when he was first interviewed at the hospital. He said that for quite a while he had had the feeling that things had changed and that the change occurred in objects outside of him as well as in his own body, and even in his own thoughts. Everything in him felt as if it were artificial. "I feel as though I have a peculiar body. My head and bones do not feel natural. It seems as if they move on hinges." He said that this feeling was particularly marked in his eyes and teeth; at one time he thought it was because of the change in his eyes that things outside appeared unnatural. When asked as to the nature of the change, he said that it was mostly "a feeling" that the world was not real, but at times it became even more tangible. On such occasions the changes could be expressed, for instance, in terms of space distortions: "Some people look taller and others shorter than they should; some are thin and others are broad." The time relationships of events seemed to have changed. When he was told, for instance, that it was 10:30 a. m., he insisted that it could not be more than 8 a. m. On another occasion he expressed himself as follows: "Sometimes when I do something that I know should take a certain length of time, it may appear to me either much longer or much shorter than it should. I know it takes me about fifteen minutes to make up the bed, and yet sometimes I feel as if it took me several hours. At other times it does not seem to take any time at all." When questioned as to what he thought caused this inability to judge

1. Schilder, Paul: Introduction to a Psychoanalytic Psychiatry (Nerv. and Mental Dis. Monogr. Ser. 50), Washington, D. C., Nervous and Mental Disease Publishing Company, 1928.

time, he answered: "It all comes back to what I am thinking about or what I feel at the time when I do the work. Sometimes it just continues on and on, and it seems as if I go through ages and ages."

Although the history first obtained seemed to point to this condition as having developed acutely, subsequent investigation showed that it was of a rather slow onset. The patient was born in the United States. The family history was without significance, the home environment having been of a pleasant and wholesome type. According to the parents the physical condition of the patient was excellent at all times, and he had never had any serious illness. Intellectually he developed satisfactorily, and at the age of 21 he was graduated with highest honors with a degree of B.S. He had been teaching physical education ever since graduation. He was a good athlete throughout his high school and college years, playing on the football and hockey teams. He was well liked by all his friends and until about the last two years he did not show any peculiar characteristics in behavior. The patient himself, however, stated that as a child he had been sickly and it was because of that that he went in for athletics. "I wanted to be like Teddy Roosevelt. I thought I was not as good as others and could better myself by physical exercise." On further questioning, one found that the feeling of physical inferiority was on a sexual basis, that very early—in fact the patient does not remember at what age—he began to masturbate; he practiced it frequently until four or five years before admission. He always worried about it, feeling that it rendered him inferior to other boys. He could not overcome the tendency, and therefore went in for athletics. On first entering college he spoke about this difficulty to the professor of physical education, and was advised to take physical exercises and "try to forget" about his sex urges. The patient increased his interests in athletics, but did not overcome the habit. About five years before admission to the hospital, he first began to take an interest in the opposite sex; until admission he had had love affairs with ten girls. In each case he had started to go out with the girl and had thought seriously of marrying her, but after a while had suddenly broken with her. He claimed that through this period he had had few auto-erotic experiences; that he was trying to fight the habit, but at the same time felt he was not normal heterosexually. On a few rare occasions when he attempted heterosexual intercourse he had ejaculatio praecox; this made him feel even more than ever that he was sexually inferior. About the time when he began to have these experiences with the opposite sex, he began to feel a gradual change in himself. He felt that he was getting weaker physically, and that he was losing power of coordination. He could not play as well on the teams as previously, and sometimes would have to stop playing in the middle of a game because of lack of coordination. His attitude toward the girls with whom he was going out was peculiar; it presented a combination of fear that the girl was "out to get me, to have me marry her," on the one hand, and on the other hand, a feeling that his salvation lay with them. This was especially noticeable in his attitude toward the last girl with whom he had gone out. She also was the first girl to notice an externally apparent change in him. On many occasions while with her he behaved peculiarly, sometimes making crude and rather childish sexual advances although he never made any attempt at intercourse. At other times his attitude was almost that of worship; he had on several occasions told her that for the last five years he had been undergoing a mental change and that she was to be the one to save him. For the last few months before admission he had seemed in a daze, and to such an extent that the people at the college in which he was teaching, as well as the girl with whom he was going out, noticed it

definitely. He was advised to take a rest. He left the college and went home; after a short time the acute excitement occurred which brought him to the hospital.

The feeling of unreality persisted for some time after admission, and was expressed by him in the same fashion as that already described. Then it gradually began to fade, giving way to a somewhat bizarre, loosely connected delusional elaboration. The development of this system was gradual. The patient said that even before admission, as far back as the early days of the onset of his condition, he was aware that there was something abnormal going on within him and felt that there must be some simple solution for it. He also had the feeling that his sexual discrepancies were in some way connected with the state of affairs, and that the key for a solution was to be found in some rearrangement of his sexual habits. He had always been much interested in mathematics and began to search for some geometrically expressed formula of the love life that would apply to his case. He was at the hospital when he gradually began to evolve this formula in his mind, a formula that in its essentials was concerned in creating some fundamental basis for life and love in their simplest forms.

What followed in the development of the case appeared as a jumble of symbols popping up at different times and on different occasions, apparently showing no connection with one another; yet a great many of them were apparently representative of emotional conditions of the patient at such times. He began with the idea that his fraternity letters, Alpha Sigma Phi, representing as they do a symbol for the brotherhood of men, could be regarded as the simplest expressions of the sum total of his love experiences. He thought that alpha represented the beginning of all things, the simplest form of life and the simplest form of love, and was comparable to the simplest form of motion, that of a piston in an automobile; smilingly he added: "This may make you think also of masturbation." Sigma, which he represented alternately as the Greek letter (Σ) and as an inversion of it when turned horizontally, would represent W and M, the initials of his own surname and that of his girl. Put together back to back (ΣΣ) the symbols represented marriage. Phi (φ) was the symbol of femininity, the final goal of love, the heterosexual experience, because it also was comparable to the usual symbol for the female sex (♀). He gradually elaborated this theory, picking up objects in his environment that gave further material for the formula. For instance, an ornament in the general dining room, consisting of a large wheel with a cross bar at the lower end, on which were a number of artificial, electrically illuminated candles, was regarded by him as representing the highest attainment of love, similar to phi in his fraternity letters, and also the most complex form of motion as evolved from the simple alpha. At the same time he volunteered that the ornament represented a rose bush, and could even represent the female genitalia. This ornament, he felt, was representative of the highest goal in his love life; at present, however, his field being limited, he found a substitute for the final goal in the brotherhood of men for which the fraternity symbols stood. In other words, he could go on feeling love and affection for the men on the ward around him, and so gratify his desires for heterosexual love. He justified this by the fact that the wheel in the ornament could be broken into two halves by an extension of the cross bar, whereby he could obtain a letter K. This letter would again represent the brotherhood of men because it stood for the male reception ward in which he lived. Numerous other objects around him were picked up as representing solutions of his problem; all of them were poorly veiled, coarse allusions to different forms of sexual gratification, and he himself suggested the possibilities. It was, however, only a stage in development.

Gradually he withdrew further and further into himself. His attitude toward other men on the ward, which was at first sociable, changed into a sullen, sulky shrinking into himself; his feelings of unreality gradually faded as this condition developed. At the time of writing he has reverted again to auto-erotic practices and has little to do with anybody on the ward, but when an attempt to draw him out of his shell is successful he talks about perfecting his geometrically expressed formula for life and love; he says that this has many wonderful possibilities. He would like to get out into the world now, spreading this idea which he knows will help people to understand each other better, will foster better feelings, will do away with war, etc.

Summary.—In this case one is dealing with a person who, starting out with a conflict on the basis of an inability to emancipate himself from an auto-erotic level, breaks down at the point when the conflict reaches its highest peak, that is, at the time when he is called on to adapt himself to a mature sexual life. At this stage there is a gradual development of the feeling of a change that is going on in him and that affects his ability to perceive himself, as well as things outside of him, as they really are. This comes to a climax in a feeling of unreality in all environment and himself. A search for a solution ensues; following it there is the beginning of a development of a delusional system.

As an example of the next step in depicting this behavior anomaly, I am presenting a brief review of a case that I reported on a previous occasion.[2] In this case a somewhat similar feeling of unreality, but of a more acute onset, led to a rapidly progressing process which, at the present time, has practically reached its final stage.

Case 2.—L. D., a young man, following a period of auto-erotism in early adolescence attempted to break away from this manner of gratifying his sex urge by the establishment of heterosexual attachments. Several attempts failed, partly because he was afraid that the girls were exacting and wanted to "tie him up to them," and partly because occasional attempts at intercourse were unsatisfactory. His attachment to the last girl was broken in a rather stormy scene, and the patient reverted to auto-erotic practice. During this last period, he began to develop numerous hypochondriacal ideas. He thought that his nose, eyes and cheeks were changed, that he was growing weaker physically, and that he was gradually wasting away and going to die. A more detailed description of his feeling of dying, however, brought out the fact that he was not dying physically but that his feelings were leaving him; the food tasted unnatural. He lost interest in other people and in the world in general, etc. This led to an acute catatonic stupor from which the patient came out, after a short time, with a fairly well connected delusional system. He thought that a group of telepathists were helping him and bringing him back to the world, and that they were sending him messages by mental telepathy. These delusions began during the catatonic stupor. At first the messages contained accusations and allusions to crude homosexual and auto-erotic acts, but as time went on they began to tell him that he was to bring into the world something new and of great importance. As the delusions developed,

2. Malamud, William: Psychoanalytic Mechanisms in Clinical Psychiatry Am. J. Psychiat. **8**:929, 1929.

the feeling of unreality gradually faded away. At the time when the case was first reported, the patient was still actively delusional and hallucinated. Since then and to the time of writing, however, he has made a fairly good adaptation to the hospital. His hallucinations have practically disappeared, leaving behind a feeling that the experiences he has lived through have endowed him with certain abilities that he did not have before the onset of the psychosis. He said that he has an ability to visualize things which are not actually objective, an ability that other people do not seem to possess. "I can think of a house in the country with beautiful gardens, and as I think of this I can see it before my eyes." His description of pictures of this type are vivid. He hints rather vaguely about some connection between this ability and his experiences with the mental telepathists. He thinks that his ability will help him a great deal when he gets out of the hospital, and that he would be willing to try and teach other people how such conditions can be reached.

Summary.—In this case, again one finds developmental conditions similar to those in case 1; but the feeling of unreality comes on more acutely and is followed by a more acute and rather stormy extrication from this feeling. The patient lived through a psychotic episode, the acute symptoms of which gradually faded out just like the feeling of unreality which they replaced; in their turn they gave way to a more or less immature appreciation of life, characterized by some loss in differentiation between objective and subjective values. One may speculate at this point on whether the patients' new ablity to visualize wishes so readily may not lead to a more complete breakdown in later life.

Finally, I am presenting a third case in which the whole process is of much more abrupt onset and cessation.

CASE 3.—E. E., a married woman, aged 40, was brought into the hospital because of an agitated depression. Her early life, up to marriage at the age of 23, was not well known but appeared to have been insignificant, the only factor of importance being that the father was a rather irresponsible person who deserted the family on several occasions. According to the patient, her father was a "cold man, who never expressed any feelings" toward her. Her marriage to a man considerably older than herself was not a happy one, and there was much quarreling. Six years after marriage she passed through an acute psychotic episode in which she presented a picture more or less similar to the one shown at the time of admission, and during which she was confined to a state hospital for three and a half months. She made a fairly good recovery, although, according to outside information, one learned that she had shown a gradual change in personality ever since, changing from a pleasant, even-tempered person to a stubborn, melancholy, hypochondriacal person. The present attack came on rather acutely. The exact nature of the precipitating cause is not well known as the history was obtained from the patient herself. She was divorced from the husband about five years previous to admission; recently she had had an affair with a man who was staying in her house. She said that this was her only extramarital experience. About a month before admission she had missed a menstrual period; a physician placed a tampon and rubber tubing into the genitalia for the purpose of abortion. She was working in a factory during this time; while there the tampon and

rubber fell out. She went for an examination to the physician who had originally inserted it; he told her that she was quite well again and need not worry. She kept on worrying about it, however, and gradually developed the idea that the tube was still in the uterus. At the time of admission to the hospital she complained of feeling depressed. Further questioning, however, revealed that the depression was really a feeling of "distance" between her and everything outside of her. "I am losing strength of mind. Something is taking the strength away from my memory. I am getting away from responses. I feel far away from everybody, away from love." When questioned whether she felt discouraged or sad, she answered, "No, not that, but I feel that I am parted from passion and from God, and it is all because of the tube in that organ (uterus). It has been growing larger and now is pressing against my brain." She felt that she had no "relation" to other people; that something had come between her and everything outside of her. This something always referred to the uterus, which, as she said, seemed to have absorbed all her interests and her feelings. She warned the physicians that if the uterus was not helped in some way or other some calamity would take place in a short while. "Now I live and love on memory, but something is taking the strength away from my memory, and when I lose it I will be like a person who has lost the past and lives on observation."

She gradually became more and more restless and confused, and began to write bizarre letters to the physicians of the hospital, begging for help in the form of an operation on the uterus. These letters contained crude allusions to sexual matters. "Give me the code and give it to me right. Give me an operation on the uterus. I am getting away from the world and living on memories and pictures. Bell had that code (Bell is the man with whom the patient was supposed to have had the affair). Reach out and save me." Her behavior in the ward too was highly erotic. In the course of a few days she went into a complete catatonic stupor which lasted about two months; during this time she had to be fed by tube. She was at times mute and negativistic, and at other times excited and voluble. Quite as abruptly as she went into the stupor she came out of it with a bizarre conglomeration of delusions and vivid erotic hallucinations. She complained of snakes crawling over her body, and of men coming into her room to assault her. This period, however, was also of short duration. She gradually, if reluctantly, began to come back to her previous level, still retaining a somewhat perplexed and emotionally shallow attitude to the whole affair. Finally she improved to the extent that she was allowed to go out. Her mental condition, however, showed a definite defect in the emotional field. Her attitude to the attack was rather superficial and she said that at times she was sorry that she came out of the condition she was in following the stupor.

In this person the feeling of unreality came on acutely and had an abrupt cessation, leaving, however, a defect in the form of emotional shallowness.

COMMENT

The feeling of unreality in the three cases differs in the degree and the intensity with which the whole personality is involved, and also in the manner in which it is replaced by other types of reaction. It is not my purpose, however, to discuss the variations in this form of experience and their relationship to special disease entities during the course of which they may occur. Suffice it to say that one finds these

experiences, with varying degrees of intensity and followed by different types of reaction, in neuroses as well as in psychoses, in the manic-depressive as well as in the schizophrenic group. In rudimentary form, furthermore, one meets with similar experiences even in normal persons, a fact to which I shall return later. Instead of describing the different degrees of the feeling of unreality and classifying them according to their diagnostic or even their prognostic values, one might try to understand this form of reaction in terms of its evolution and relationship to the personality of the patient. The approach could be made from two directions. One could study: (1) the personal value of the experience, that is, its relationship to the development and totality of the personality in which it occurs, and (2) the impersonal value, that is, the relation of this experience to allied reactions that occur within the limits of the normal.

First, one may see how the reaction has developed in the cases here presented. Clinically, the persons in the three cases experienced a conflict in emotional life at a certain stage of development. At a period when normally the person should take up heterosexual activities, they found themselves unable to emancipate themselves from infantile methods of gratification, that of auto-eroticism (in cases 1 and 2 this is clearly seen from the histories given; in case 3 it is probable that there was an auto-erotic element because of the marked fixation of interest on the uterus). In other words, a conflict is staged between unconsciously motivated emotional desires directed toward the ego and the conscious appreciation of what is demanded by conventional standards of normal behavior. This issue in this conflict is therefore furnished by the direction of the flow of the sum total of emotions, or libido. The outcome in the conflict in these cases is a decision in favor of the ego, which means that all emotional attachment to the outside world is abstracted and turned inward, a condition frequently observed in psychoses. This complete inversion of interests (as represented by the stage during which the patient severs actual relations with the outside, as in catatonic stupor) persists for a shorter or longer period of time, and is replaced by a more or less successful attempt to regain the outside world by means of a compromise. This compromise, as I have discussed more fully in a previous communication, takes place between the ego interests and whatever social and environmental standards (ego ideals) are still left functioning, this being the condition in which all the patients are left after the acute episodes. At the point just preceding this compromise, namely, when the emotional attachments to the outside are gradually being withdrawn, and as these are being directed toward the ego, one finds the feeling of unreality coming on and lasting until the compromise is brought about. Schilder, following Freud's trend of thought, has advanced the hypothesis that the

feeling of unreality is brought about by the appreciation of the fact that libido is being withdrawn from the outside at a time when the normal standards of appreciation of environment (ego ideals) are still capable of rendering judgment, and, so to speak, inform the perceptive powers of the incongruity. I shall discuss here this hypothesis and show how the different clinical pictures, as well as some experimental work in neurophysiology and psychology, point to the practical applicability of the theory.

Before doing this, however, it will be well to clarify what I understand by "reality" and just where in this function I believe the disturbances in these patients occur. Psychologically, one should understand, under reality, objectivity, in which objectivity is regarded as a projection of sensations onto something outside, the nature of which one has no means of knowing. Thus, then, one can say that the reality to which I am referring is a relative or phenomenal one as contrasted with an absolute reality of something that is impersonal and unintelligible. (Philosophically, such absolute reality would coincide with the "Ding an Sich" of Kant.) The exact definition of the relationship between these two has always been much disputed both in philosophic and in psychologic literature. One of the clearest statements on this subject, and to my mind as yet unsurpassed, is found in Plato, expressed in a fashion which helps materially in approaching the discussion of this subject. I am referring to the cave allegory, at the beginning of the seventh book of the Republic.[3] Following a discussion of the four methods whereby cognition is gained and the relative value thereof, Socrates proceeded to give a graphic illustration of such methods as follows:

> Behold men, as it were, in an underground, cavelike dwelling, having its entrance open towards the light and extending through the whole cave. These persons are fastened down from childhood with chains on their legs and necks, and must always remain in the same position with their backs towards the entrance, and staring directly ahead of them towards the opposite wall. They cannot turn their heads either sideways, upward or downward. Their light comes from a fire that burns above, afar off and behind them. Between the fire and those in chains there is a road along which one may see a low wall similar to the stages of conjurors that are built before the people to whom they show their tricks. By the side of this low wall men pass by carrying all sorts of machines. Rising above the wall are statues of men and their animals wrought in stone. . . . The chained men, therefore, are unable to see anything either of themselves or of one another, or of what passes by outside the entrance except the shadows that fall from the fire on the opposite side of the cave.

Socrates described further how, after some time, these persons in the cave, thinking that the shadows on the wall are the real things, will

3. Plato: The Republic, Translated by Henry Davis, London, George Bell and Sons, 1904.

gradually build up rules and laws governing the successions of these apparitions on the wall, and by that gage their own activities, and foretell what they themselves, as well as the others, will behave like under certain conditions. This form of cognition that concerns itself with phenomena or shadows of the absolute real, and the establishment of a certain orientation in such a world is, of course, developed in an empiric fashion. Plato, who considers this from the philosophic point of view as a very relative and inferior form of gaining insight into things, described further how one of the prisoners, when freed and permitted to turn around and perceive the light and then gradually ascend through the opening into the real world with the skies and sunlight, will at first be blinded by the change, but afterward will learn to see the real nature of things. In psychologic studies, however, one must regard the phenomena or the shadows on the wall as real in everyday life; all standards of orientation in life must be regarded as being developed on the basis of just such empiric knowledge. The psychoanalytic theory, as well as some experimental work that I shall mention later, gives one some insight into the nature of the development of this empirically gained orientation in relative reality. Freud, in his "formulation regarding the two principles in mental functioning" [4] in a rather schematic way presents the psychoanalytic view of such an evolution. In his development, man starts out with a store of unconscious mental processes in which the guiding principle is that of pleasure-pain. With this equipment he faces the outside world in which certain demands are to be complied with in the interests of the continuation of his existence. At times the demands run counter to the desires of the unconscious processes, and on such occasions it becomes necessary to repress these desires. Gradually the environmental demands are built into a unit which always represents a judge and repressor. This is the super-ego, or ego ideal. The other side, that is, the sum total of unconscious processes, could be looked on as constituting the id. Between the two and constantly probing them, weighing their relative importance and considering the advisability of compliance with them, is the third factor, the ego or perception ego. It approves wholly of neither the one nor the other, but always settles on a compromise between the two. This compromise, therefore, is guided as much by the demands of environment as it is by the pleasure principle. It is of a later development, and because it takes into consideration the objective values it can be regarded as guided by the reality principle, in health as well as in disease. In this compromise, at any given time, then, there is a constant balancing of two forces, that of the id directed

4. Freud, S.: Formulation Regarding the Two Principles in Mental Functioning, Collected Papers, London, Hogarth Press, 1925, vol. 4.

toward the pleasure attainment, and that of the ideal ego, or environment, repressing the tendency if it comes into clash with it. All conscious perception is really governed by this compromise with the reality principle. In a previous communication,[5] in discussing this form of perception (which I consider the only mode of cognition that should be considered as perception), I attempted to show that it is limited to conscious awareness of things in time and in space, analogous to the phenomena of Kant and the shadows of Plato. One learns from the description given of the psychoanalytic concept of such a mode of cognition that it develops empirically and on the basis of a compromise between two opposing forces. In the aforementioned communication,[5] I reported the results of experiments concerning the effect of different types of sensations on the perception of objects in space. I found that, given objectively equal distances, the perception of these by an isolated organ of sense, in this case the cutaneous, will depend on the nature of the stimuli bounding these distances. Thus, the distances between two indifferent tactile stimuli was perceived as being larger than an objectively equal distance bounded by two painful stimuli. Observations of similar nature were reported by von Skramlik,[6] in determining thresholds and by Warden and Flynn[7] in the optic field. On the basis of all these observations I came to the conclusion that the appreciation of contents in space and in time is influenced by subjective emotional values just as much as it is by empirically gained objective standards. The latter serve as a constant force of repression to the former, but need for their proper functioning the normal unimpeded activity of the whole sensory apparatus. The apparatus can be looked on as the perception ego, and whenever any part of it is shut out, the emotional influences gain the ascendancy and perceptions are formed that are not true when measured by the reality principle. In my experiments, for instance, when the visual sense was shut out and the only means of perception left was the cutaneous sense, the pleasure-pain principle gained the ascendancy over the objective empirically gained standards, and the comparison of distances depended on whether they were painful or not. When the eyes were opened, the ordinary state of affairs returned and distances could be measured in the usual way. A further substantiation of this trend of thought was recently furnished by Weber and Dallenbach[8] who, in a series of ingenious experiments,

5. Malamud, William: The Rôle Played by the Cutaneous Senses in Spatial Perception, J. Nerv. & Ment. Dis. **66**:585, 1927.

6. Von Skramlik: Ztschr. f. Psychol. u. Physiol. d. Sinnesorg., 1925, 2.

7. Warden, C. J., and Flynn, E. L.: Effect of Color and Arrangement on the Apparent Size and Weight of a Package, Am. J. Psychol. **37**:398, 1926.

8. Weber, C. O., and Dallenbach, K. M.: The Properties of Space in Kinaesthetic Fields of Force, Am. J. Psychol. **41**:95, 1929.

found the following: (1) a given area sensed under load appears to be phenomenally enlarged; (2) a given angle traversed under load appears to be phenomenally more acute; (3) a given arc traversed under load appears to be phenomenally more sharply curved. In these experiments, then, the greater or lesser ease with which a figure is traced "distorts" its objective size and shape.

From both angles, that is, on the one hand by the psychoanalytic method of approach, and on the other by experimental investigation in the laboratory, one converges to one conclusion: The conscious perception of contents in space and in time, that is, of phenomena, is gained by experience and depends on a balancing between the two factors, subjective values and objective stimuli. The reality thus built up is a relative one and within certain limits fluctuates between influences of both sides. For the proper balancing of reality appreciation, therefore, standard conditions on both sides are needed. If one influences either one by decreasing or increasing it, the normal state of affairs will change and appreciation of reality will be distorted. In experimental work, for instance, one willingly decreases the power of the repressor and allows the emotional or subjective factor, which here remains unchanged, to gain ascendancy. People can, and do, at will return to the usual status by correcting this (opening the eyes). Conditions, however, are different in a case in which the discrepancy is caused by an unusual increase in the emotional component but in which the repressor remains as before. On such an occasion, too, there is a distortion in the perceived contents in time and in space, but here the repressor has not been experimentally decreased and therefore cannot voluntarily regain ascendancy. The resulting condition is one in which the perceptive ego becomes aware of the fact that things in the perceived world are not up to standards previously laid down; in other words, a feeling of unreality. This is especially well illustrated in the descriptions of experiments with mescaline.[9] In case 3 one finds that just such a condition exists. During the early stage of the disease, when there was no intellectual deterioration, and when the ability to appreciate environmental demands was still intact, that is, when the ego ideals had not yet been broken down, the repressor remained as before. The subjective emotional factor, however, has been increased. There was a gradual withdrawal of affections and emotional attachments from outside objects and a turning of them unto the patient's own self. This was especially well expressed in the ramblings of this patient. It was her interest in the uterus and the gradual increase of this organ (as she termed it, the

9. Mayer; Gross, W., and Stein, J.: Ueber Stoerungen des Raumsinns und des Zeitsinns unter Mescalinwirkung, Vortrag, ver. f. Psychiat., Düsseldorf, 1926, in Zentralbl. f. Neurol. u. Psychiat. **45**:519, 1927; also a personal communication to the author.

organ of love) that conditioned the "distance . . lack of response . . ." It was because of this that she was torn away from the outside and "lived and loved in memory." The memory, which really represented the still intact environmental standards, informed her of what she should feel like, or rather of what she felt like before. The enlarged uterus, however, representing the sum total of emotional desires turned toward herself, made things appear distorted, different from what they should be according to her memory. Here, therefore, one reaches a situation that is to a certain extent similar to the infantile stage, when there is a conflict between the two forces, subjective and objective, but with this difference, that here there is a memory and it is memory that conditions the feeling of unreality. The degree of intensity of this feeling differs, of course, and so one finds that in the most serious of the three cases reported, case 1, it reaches the point where actual time and space distortions are clearly evident. The principle of development, however, is the same in all three cases. This feeling will persist while the conflict goes on, and until one of the two opposing forces gives way. In some conditions, the ideal ego or outside world may gain the supremacy again. One finds such a condition, for instance, beautifully illustrated in the mescaline intoxication experiments. The other alternative is that the emotional forces will be victorious and the ego ideals will break down, or that all the environmental standards that come into clash with the emotional desires will be disregarded and a new attitude to the world will be established. One finds such a condition of affairs in case 1 especially, in which there is a building up of a childish attitude to the world, an attitude governed by early ideals endowed with magic powers. These new standards replace the prepsychotic, more mature ones, and as they do not oppose childish methods of emotional gratifications they can remain and serve as the basis of the compromise. The new standards, furthermore, being of a more primitive type ontogenetically and not coming into clash with the newly established subjective factors, will remove the feeling of incongruity or unreality that the more mature standards have conditioned.

An approach of this type makes the symtoms or, as I would prefer to regard them, the reactions and experiences met with in mental disturbances intelligible in terms of reaction to actual situations. It is understood, of course, that the number of facts observed both in the study of the special senses and in the clinical investigations is, as yet, insufficient to make the interpretations anything more than a useful working hypothesis. The observations made, however, stand as such and they point the way for new methods of approach in the study of mental diseases.

MULTIPLE LUMBAR PUNCTURES

THEIR VALUE FOR THE LOCALIZATION AND DIAGNOSIS OF TUMORS OF THE CAUDA EQUINA *

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In a paper on the diagnosis and localization of new growths and inflammatory lesions in the lowest parts of the vertebral canal, one of us (C. E.) with Dr. Constable [1] reported on experiences in forty-five cases of tumor and radiculitis, in twenty-eight of which tumors had been found between the roots of the cauda equina. In that paper mention was made of the use of lumbar punctures at several levels, with comparative manometric tests and examination for total protein of the fluid withdrawn from the different loci. The study showed that in both extradural and intradural tumors of the cauda equina, whether a subarachnoid block could be demonstrated or not, the total protein in the spinal fluid was always found well above the normal. This led to the conclusion, among others, that if the total protein in the fluid obtained by lumbar puncture was within normal limits, the diagnosis of "neoplasm in the lowermost parts of the vertebral canal" was not justified.

It is well known that, based on the neurologic symptoms and signs alone, the localization of tumors of the cauda equina is often difficult. It is frequently impossible to determine with certainty whether the growth is situated near the origin of the affected roots from the spinal cord, or whether it is more caudad near the exit of the roots from the vertebral canal. For this reason, the exact localization by an injection of iodized poppy seed oil—40 per cent—was considered essential and almost always indicated. At the meeting of the American Neurological Association held in 1928, all those who took part in a discussion on the value of iodized oil [2] coincided in the expressed belief that iodized oil was of especial value for the localization of tumors of the conus and cauda equina. We confess that, until recently, we held the same view.

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* From the Surgical Division of the New York Neurological Institute.

* Read at the meeting of the Society of Neurological Surgeons, Dec. 2, 1929.

1. Elsberg, C. A., and Constable, K.: The Differential Diagnosis of Tumor and Inflammatory Diseases of the Cauda Equina, Arch. Neurol. & Psychiat. **23**:79 (Jan.) 1930.

2. Globus, J., and Strauss, I.: Intraspinal Iodolography, Arch. Neurol. & Psychiat. **20**:1331 (June) 1929.

Our experiences with multiple lumbar punctures have, however, convinced us that by this simpler procedure it is possible to localize tumors of the cauda equina with as much certainty as by an injection of iodized oil, and therefore to avoid the injection of a foreign substance which has certain distinct disadvantages.[3]

We do not desire to enter into a discussion concerning the uses and abuses of the iodized oils, which in many neurologic clinics abroad and in some in this country are now considered almost indispensable aids in the localization and diagnosis in all or most cases of compression of the spinal cord and roots of the cauda equina. The value of the method of Sicard and Forestier has been attested to by many writers. But we are strongly averse to its indiscriminate use as a "short cut" to diagnosis and localization, and fear that the information so easily to be gained by its injection has, in the views of some, lessened the real necessity for repeated careful neurologic examinations, and for thorough pressure and chemical studies of the cerebrospinal fluid.

As far as the injections of iodized oil for the localization of tumors of the cauda equina are concerned, we have, after its use, observed several patients who suffered for a number of days from severe root pains, and in whom for the same period vesical disturbances became much aggravated. In three patients, the iodized oil was arrested by arachnoid adhesions and by dislocated nerve roots, several vertebrae higher than the upper level of the tumor. At operation we have, as have others, often seen acute inflammatory changes in the nerve roots and sometimes a fresh fibrinous exudate on the roots and leptomeninges after the injection of iodized oil. Even though the inflammatory process and the "aseptic meningitis" soon subside, we believe that this irritant effect on the roots of the cauda equina constitutes a distinct disadvantage in the use of iodized oil.

This made it necessary to look for a better method to aid in the localization of lesions of the cauda equina, and led to the study of the procedure of multiple lumbar punctures, the experiences with which are described in what follows.

Combined cistern and lumbar punctures with pressure studies and examination of the fluid from each location, have, of course, been used by many after Ayer had devised cistern puncture and recommended combined cistern and lumbar punctures.

Double or multiple lumbar spinal punctures for the diagnosis and localization of the lesions of the cauda equina—although probably tried

3. Ebaugh, F. G., and Mella, H.: Am. J. M. Sc. **172**:117, 1926. Armour, D.: Lancet **1**:423, 1927. Craig, W. M.: Surg. Gynec. & Obst. **49**:17, 1929. Wolfsohn, J. M., and Morrissey, E. J.: California & West. Med. **26**:55, 1927. Sharpe, W., and Peterson, C. A.: **83**:32, 1926. Lindblom, A. F.: Acta radiol. **5**:129, 1926. Desgouttes, M. L.: Bull. et mém. de la Soc. Nat. de Chir. **53**:14, 612, 1927. Schönbauer: Deutsche Ztschr. f. Chir. **198**:211, 410, 414, 1926.

by others—have, to our knowledge, been mentioned only by workers in this and one other clinic.[4]

The first patient in whom, by means of double lumbar puncture, one of us was able to diagnose and to localize exactly an extradural chondroma which compressed the roots of the cauda equina, was operated on in 1926.

REPORT OF CASE

The patient, a man, aged 46, was referred to the Neurological Institute as a private patient by Dr. S. P. Goodhart, of New York City. He gave a history of pain in the back and lower limbs for six months, and of increasing weakness in the right lower extremity. The neurologic disturbances consisted mainly of loss of power to flex the right foot dorsally, loss of both achilles reflexes and marked diminution of sensibility over the sacral dermatomes on the right side.

The diagnosis of tumor was considered certain, but there was much uncertainty concerning the exact location of the growth.

A lumbar puncture was done below the fourth lumbar spine; this showed a complete subarachnoid block and only a few drops of fluid were obtained. Another lumbar puncture was then done below the second lumbar spine; manometric tests showed no evidence of any block, but the fluid that was withdrawn contained 130 mg. of protein and a 2+ globulin reaction.

It was certain, therefore, that the subarachnoid space was obstructed by a tumor between the second and fourth lumbar vertebrae.

In order to gain additional support for the results of the two punctures, 1 cc. of iodized oil was injected through the needle in the first lumbar interspace. The roentgenogram showed that the iodized oil had been arrested at a level which corresponded to the middle of the third lumbar vertebra. At the laminectomy, the arches of the third and fourth lumbar vertebrae were excised, and a large soft extradural chondroma was removed from this region.

The location of the new growth was so satisfactorily determined by the two lumbar punctures that the decision was made to use this method as a routine for the localization of tumors of the cauda equina. Table 1 gives a summary of our recent experiences. In the earlier cases, we still controlled the localization that had been determined by double or multiple punctures by an injection of iodized oil, but in our recent cases, we have depended entirely on the information gained by punctures at two or more lumbar levels.

TECHNIC

Double puncture may be performed in one of several ways:

1. A needle is first introduced below the fourth (or fifth) lumbar spine, and all of the manometric tests are made and the results charted ("touch" compression over the jugular veins, deep compression, straining, removal of 7 cc. of

4. Stookey, B., and Klenke, D.: A Study of the Spinal Fluid Pressure in the Differential Diagnosis of Diseases of the Spinal Cord, Arch. Neurol. & Psychiat. **20**:84 (July) 1928. Cushing, H., and Ayer, J.: Xanthochromia and Increased Protein in the Spinal Fluid Above Tumors of the Cauda Equina, Arch. Neurol. & Psychiat. **10**:167 (Aug.) 1923.

fluid, determination of the new level of the fluid in the manometer). The fluid that has been drawn off is saved for chemical and microscopic study and the needle is removed.

With a fresh needle, the vertebral canal is punctured below the first (or second) lumbar spine, and all of the tests are repeated at this level, and the fluid withdrawn is marked separately and saved for laboratory examination.

2. More reliable results will be obtained if the spine is punctured successively in two locations—one needle below the fourth (or fifth) and the other needle

TABLE 1.—*Double Punctures in Ten Cases of Tumor of Cauda Equina*

Case	Upper Vertebral Level and Type of Tumor	Level Shown by Iodized Oil	Manometric and Cerebrospinal Fluid Observations		Spines and Laminae Removed at Operation
			Upper Puncture	Lower Puncture	
1	L3 and L4; chondroma	L3	L2; no block; fluid clear and colorless; protein, 130 mg.; globulin, 2+	L4; no fluid obtained	L3, L4
2	L2; perineural fibroblastoma	L2	L1; no block; fluid clear and colorless; protein, 45 mg.; globulin, 1+	L4; incomplete block; xanthochromia; protein, 300 mg.; globulin, 4+	L1, L2, L3
3	L5; fibroangioma	L3	L1; no block; slight xanthochromia; protein, 75 mg.; globulin, 2+	L3, L4; complete block; no fluid obtained severe root pain	L3, L4, L5
4	L2, 3, 4; lipofibroblastoma	Not used	L1; partial block; slight xanthochromia; protein, 300 mg.; globulin, 4+	L4; complete block; bloody fluid	L2, 3, 4, 5
5	Myeloma	Not used	T12; no block; fluid clear and colorless; protein, 100 mg.; globulin, 2+	L5; complete block; xanthochromia; coagulation	
6	L2; chondroma	Not used	L1; no block; fluid clear and colorless; protein, 50 mg.; globulin, 1+	L3, L4; complete block xanthochromia; protein, 150 mg.; globulin, 2+	L2, L3, L4
7	L2; medulloblastoma	Not used	L2; complete block; needle in tumor; pure blood obtained	L3, L4; complete block bloody fluid	L2, L3, L4
8	Bone changes up to L4; metastatic carcinoma	Not used	L2; Partial block; protein, 44 mg.; globulin, 1+	L4, L5; partial block; protein, 50 mg.; globulin, 1+	
9	T11, 12; extradural tumor, unclassified	Not used	L2; complete block; xanthochromia; protein, 300 mg.; globulin, 4+	L5; complete block xanthochromia; protein, 300 mg.; globulin, 4+	T11, 12, L1
10	L2 to L5; ependymal glioma	Not used	L1; no fluid; root pain	L4; no fluid; root pain	L2, 3, 4

below the first (or second) lumbar spine. The pressure readings and removal of fluid from each needle are done simultaneously (table 1, case 6, chart).

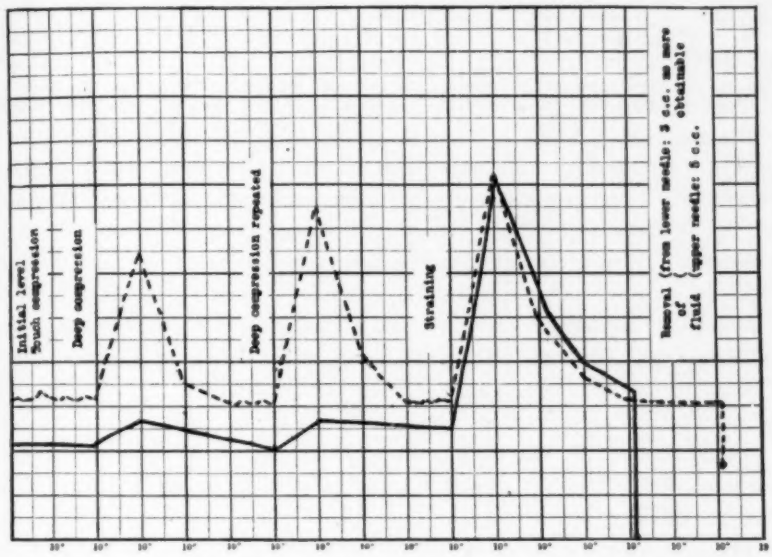
COMMENT

The first puncture may be made below either the fourth or the fifth lumbar spine, and the second, below the first or the second spine. To a certain extent, the spaces selected for the punctures depend on the clinical symptoms and signs. One may, however, make one or more additional punctures if considered necessary. As the skin and subcutaneous tissues are well anesthetized with procaine hydrochloride, the multiple punctures do not cause additional pain.

If the manometric estimations made through the lower needle demonstrate a positive subarachnoid block and those made through the upper needle show no block, the obstruction in the subarachnoid space lies between the first and the fourth (or second and fifth) lumbar vertebrae.

If, however, the tests at both levels demonstrate a block, then a third puncture should be made below the spinous process of the twelfth thoracic vertebra. An absence of block below the twelfth thoracic vertebra and the presence of a block at the second lumbar vertebra indicate that the neoplasm lies between the levels of these two needles.

The absence of any block in punctures made as low as the fifth lumbar vertebra signifies that if there is a tumor, it is located below



Observations in the case of a chondroma at the level of the second lumbar vertebra. The broken line indicates results when the needle was inserted below the first lumbar vertebra and the solid line, when the needle was inserted below the fourth lumbar vertebra. The readings were made simultaneously.

the level of the fifth lumbar vertebra, i. e., that it lies in the sacral vertebral canal.

Failure to obtain fluid from any of the needles demonstrates that the lesion, if a tumor, is of large size and that it fills up the lower part of the vertebral canal. Patients in whom this condition is met with are usually suffering from a so-called giant tumor of the conus and cauda equina, and in these cases the x-ray picture often shows a distinct enlargement of the lumbar vertebral canal. During the performance of a lumbar puncture, the patient may complain of pain which shoots down one limb and which is due to the contact of the point of

the puncture needle with one of the nerve roots. Such an occurrence is much more frequent when there is a large tumor which fills the canal at the point of puncture and envelops the roots of the cauda equina or pushes them to one or the other side. These root pains occur especially often when no fluid can be obtained by any of the punctures at different lumbar levels.

In one patient (table 1, case 7) only a small amount of bloody fluid escaped from the needles in the fourth and fifth lumbar interspaces. Puncture in the second lumbar interspace caused marked root pain and free bleeding from the needle. The conclusion was that the patient had a large and vascular tumor which filled the lumbar vertebral canal, and that the uppermost needle had penetrated the neoplasm. At the operation, a large tumor was exposed which filled the lower part of the canal and which was so vascular that the bleeding caused by the removal of several small pieces for histologic study was controlled only with great difficulty.

The studies of the pressure relations of the spinal fluid in disease of the spinal cord made in this clinic by Stookey and his collaborators [5] have so expanded the original Queckenstedt procedure that the manometric tests now made constitute a refined series of tests for the recognition of obstruction in the spinal subarachnoid space. If these tests are done with care and the results are carefully judged, much information is gained concerning not only the presence or absence of a spinal subarachnoid block from any cause but also its degree. One of the procedures is the "pressure index"—i. e., the new level of the fluid column in the manometer after a small amount has been allowed to escape from the needle.[6]

In eight patients with new growths in the region of the cauda equina in whom double lumbar punctures were done, we made a study of the pressure indexes (table 2).

For the comparative study of the percentage of fall of the columns of fluid in the manometer tubes when a double puncture has been performed, the amount of fluid withdrawn from each needle should be the same. It was originally recommended [7] that 7.5 cc. should, if possible, always be withdrawn. This has not regularly been done; therefore the pressure indexes at the upper and lower levels cannot, in this study, be compared with each other.

When there is a complete subarachnoid block at the level of the lower needle, it is often impossible to drain off more than from 2 to 3 cc. of fluid. In these cases the new level is always at zero, and there-

5. Stookey and Klenke (footnote 4, first reference).

6. If the first level of the fluid in the manometer is less than 60 of the scale, then the removal of only a small quantity of fluid (from 3 to 5 cc.) may cause a fall to 0 or below.

7. Stookey and Klenke (footnote 4, first reference).

fore it is not so important to have withdrawn the full amount of cerebrospinal fluid.

The following conclusions may be drawn from the data recorded in table 2:

1. In tumors of the cauda equina, a puncture below the fourth or fifth lumbar spinous process with removal of fluid up to 7.5 cc. will always be followed by a 100 per cent drop in the level of the fluid in the manometer tube—i. e., to zero—whether the subarachnoid block is complete or incomplete. Not only does this occur when double puncture

TABLE 2.—*Comparative Pressure Indexes in Eight Cases in Which Double Punctures Were Performed*

	Upper Puncture				Lower Puncture			
Case	Puncture Below Spine of	Subarachnoid Block	Amount of Fluid Removed	Fall of Level, per Cent	Puncture Below Spine of	Subarachnoid Block	Amount of Fluid Removed	Fall of Level, per Cent
1	L 2	No	6 cc.	100	L 4	Complete	Only few drops of fluid obtained	
2	L 1	No	7.5 cc.	60	L 4	Partial	7.5 cc.	100
3	L 1	Partial	7.5 cc.	20	L 3 L 4	Complete	2.5 cc., all that could be obtained	100
4	T 12	No	5 cc.	80	L 4	Complete	3 cc., all that could be obtained	100
5	T 12	No	6 cc.	100	L 5	Complete	Only few drops of fluid obtained	
6	L 1	No	5 cc.	48	L 3 L 4	Complete	3 cc., all that could be obtained	100
7	L 3	Partial	5 cc.	100	L 4 L 5	Partial	5 cc.	100
8	L 2	Complete	5 cc.	100	L 5	Complete	3 cc., all that could be obtained	100

has been done but it has been observed in a large number of patients in whom only one needle was inserted. This 100 per cent drop in the new level after removal of fluid no doubt occurs so regularly because of the diminished quantity of cerebrospinal fluid in the relatively short part of the spinal subarachnoid space below a new growth in the region of the cauda equina.

2. When a puncture has been performed above the location of a tumor of the cauda equina and there is no subarachnoid block at that level, the percentage of fall until a new fluid level is reached may be 100 per cent even when less than 7.5 cc. of fluid has been withdrawn.

Double or multiple lumbar punctures are of value also for the differential diagnosis between tumors and inflammatory diseases of the

roots of the cauda equina. Not only may the presence of a block at a lower, and a free subarachnoid space at a higher level be of diagnostic significance, but the presence of xanthochromia and a higher percentage of total protein and of globulin in the fluid derived from the lower locus has great significance. As already mentioned, in tumors of the cauda equina, an increase in total protein has, in our experience, regularly occurred in new growths in this region, and the total protein was always within normal limits in inflammatory disease. If there is no subarachnoid block demonstrable at either the upper or the lower lumbar level and there is no increase of total protein in the fluid removed from each locus, the conclusion is justified that there is no tumor either in the lumbar or in the sacral part of the canal.

In tumors of the conus and cauda equina, the results of double or multiple lumbar punctures have made it possible to divide the cases into the following groups:

1. The typical case, in which a complete subarachnoid block is demonstrated by puncture through one of the lower lumbar interspaces, and no block at the first (or second) lumbar interspace. This observation signifies that the tumor is situated somewhere between the first (or second) and the fourth (or fifth) lumbar vertebrae.

2. There is a complete subarachnoid block at the fourth lumbar vertebra and a partial block at the first. This means that the tumor extends somewhat above the first lumbar vertebra but lies mainly somewhere between the first and the fourth vertebrae.

3. There is a partial block at the fourth lumbar vertebra and no block at the first. This means that the tumor lies somewhere between those two levels but is not of sufficient size to obliterate completely the subarachnoid space above the lower level.

4. No fluid obtainable at the fourth lumbar vertebra and fluid easily withdrawn and no subarachnoid block at the first. This means that the tumor lies below the first lumbar vertebra and that it is probably of large size.

5. Complete block at the fourth and at the first lumbar vertebrae. This indicates that the tumor lies near the tip of the conus. A puncture through the twelfth interspace will show whether the growth is a small one that lies between the twelfth thoracic vertebra and the first lumbar vertebra, or whether it extends higher up on the cord above the twelfth thoracic vertebra.

6. No fluid obtained by puncture through any of the lumbar interspaces. This indicates that there is a large tumor which fills up the lower part of the vertebral canal, and which may extend upward over the conus.

7. No block at the fifth and no block at the first lumbar interspace. This means that the tumor, if it is a tumor, is situated in the sacral part of the vertebral canal.

CONCLUSIONS

The diagnosis of a tumor of the conus and cauda equina having been suspected from the history given by the patient and the neurologic disturbances discovered at the examination, with an absence of x-ray changes characteristic of malignant bone disease, lumbar puncture with manometric tests and examination of the cerebrospinal fluid for total protein, will, in most instances, allow one to arrive at the certain conclusion that there is a new growth. In not a few patients, however, one cannot be certain about the location of the obstruction in the subarachnoid space and therefore of the part of the bony spine in which the laminectomy is to be performed.

The localization of the tumor can then be made by two or sometimes three spinal punctures at different levels. Injection of an iodized oil with the inherent disadvantages of that substance is unnecessary. By a double puncture it is possible, not only to localize exactly a block in the lumbar subarachnoid space, but also to come to a decision whether the block is due to a new growth or to an inflammatory process.

CAUSALGIA OF THE UPPER EXTREMITY

TREATMENT BY DORSAL SYMPATHETIC GANGLIONECTOMY *

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Pain in an extremity resulting from an inadequate supply of arterial blood is a distressing symptom. Whether the ischemia results from vasomotor spasm (Raynaud's disease), intrinsic pathologic changes of the arterial wall (thrombo-angiitis obliterans, etc.) or traumatic severance of the main artery, the pain that results is much the same in character and constitutes the chief concern of the patient. Present day surgical treatment for ischemic pain is directed toward the abolition of the vasoconstrictor control of the vessels in the part involved.

Adson and Brown,[1] in a recent contribution, dealt thoroughly with historic, theoretic and recent progress in the surgical treatment for vascular lesions, particularly Raynaud's disease. Suffice it to say that through the efforts of these authors and their associates, Raynaud's disease has joined the list of controllable maladies. The application of such principles in the treatment for pain in other circulatory conditions of the upper extremity would therefore seem justified. My report is concerned with the treatment in a case of ischemic pain (causalgia) in the arm and hand following a gunshot injury to the second portion of the axillary artery.

REPORT OF CASE

History.—L. B., an American man, aged 24, a "liquor salesman," with an irrelevant family history, had previously had excellent general health, except for a gonorrheal infection in June, 1928. He had been a heavy drinker for ten years previous to admission and had drunk about one pint of whisky daily. On the night of Oct. 24, 1928, the patient was shot with a thirty-eight caliber revolver. One bullet entered the right axillary region at the lower border of the anterior axillary fold and came out just above the middle portion of the spine of the scapula. Another bullet entered the left shoulder at the insertion of the deltoid and came out just to the left of the spinous process of the first dorsal vertebra. Immediately following the injury, the right arm fell useless to the side. There was profuse bleeding from the bullet wounds, and a large hematoma developed in the right axillary region. Intense pain in the right hand and wrist, and to a lesser degree in the left hand and wrist, started at once. At the time of first aid treatment, the local physicians noted that the right arm and hand were pale and

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* From the Department of Surgery, University of Louisville School of Medicine.

1. Adson, A. W., and Brown, G. E.: Surg. Gynec. Obst. **48**:577, 1929.

colder to touch than the left arm and hand. No radial or brachial pulse was felt on the right side. The pulse and blood pressure were normal in the left arm. The axillary pulse could not be determined because of the large hematoma. No movement could be performed in the right arm other than slight abduction of the shoulder.

The patient first came under my observation three weeks after the injury. Pain had been, and continued to be, the predominating feature of the case. He described the pain as drawing and burning. It was constant but was subject to waves of exacerbation. At no time was the pain sharp and shooting; in fact, it was not particularly severe at any one time, but the constant unrelenting nature of the pain was described as intolerable. There were no periods of freedom except when the patient was asleep after taking large doses of morphine. There was no radiation of the pain. It seldom extended above the wrists, and apparently it was most severe in the fingers and the palms. Most of the pain was felt in the right hand, but during the more severe periods it was also felt in the left hand. The character of the pain in the two hands was similar. Application of heat offered only temporary benefit. Application of a tourniquet for fifteen minutes of each hour gave more relief, but the result was only temporary. Manipulation and passive movement exaggerated the pain.

Examination.—At my first examination on Nov. 14, 1929, the following positive observations were made: The patient was lying in bed, obviously in pain, with both hands supported on a soft pillow. Any movement of the right hand caused him to cry out with pain. The right hand and forearm were colder to touch than the left, and the skin of both was moist. The color of the right hand and finger tips was pale. After the nail was pressed on, the color returned slowly, indicating a sluggish capillary circulation. The radial and brachial pulses could not be palpated on the right side. The pulse rate in the left arm was normal. The blood pressure in the left arm was: systolic, 122; diastolic, 80. Motor power in the muscles supplied by the radial nerve was absent. Motor function of the other divisions of the brachial plexus was present but markedly diminished. There were no areas of total anesthesia, but there was hypesthesia below the elbow, most marked in the hand and fingers. Gentle pressure over the right fingers and palm caused prickling pain similar to that experienced when one's hand and arm "go to sleep."

The patient was transferred to the Kentucky Baptist Hospital on November 17. His condition then was in every way similar to that recorded at my first examination, except that he complained more severely each day of pain in the hands. The laboratory examinations gave negative results, except for a moderate secondary anemia.

First Operation.—Exploration of right axilla; lysis of adhesions between the cords of brachial plexus and axillary vessels; excision of distal end of obliterated axillary artery; ligation of axillary vein; ether anesthesia.

The brachial plexus and axillary vessels were exposed by dividing the pectoral muscles at their insertion. The axillary artery was found completely severed at the level of the pectoralis minor, and the proximal end was occluded by a large organized thrombus. The distal end of the artery was collapsed. The axillary vein was intact. A large mass of scar tissue bound the branches of the brachial plexus tightly to the axillary vessels. The fact that the radial nerve was most severely involved explains the motor paralysis noted. Each division of the plexus was dissected free and each one was found intact. About 2 inches of the distal artery was excised. The proximal end of the vessel was ligated, and the axillary vein was doubly ligated and divided. Each major cord

of the brachial plexus when it had been adherent to the scar was covered with fat pads. Closure was made in layers after the divided pectoral muscles had been sutured.

Course.—For three days following the operation, the patient was relieved of most of the pain. The right hand and arm were distinctly warmer to the touch, and the part could be moved without great discomfort. With the relief from pain in the right hand came almost complete relief from pain in the left hand. After three days, however, the pain returned in its original form and severity.

Skin temperatures, taken with a clinical thermometer were recorded as follows:

	Cubital Fossa		Forearm		Palm		Between Fingers				
							Right			Left	
Mouth	Right	Left	Right	Left	Right	Left	4 and 5	3 and 4	2 and 3	4 and 5	3 and 4
99. F.	98 F.	98.2 F.	98 F.	98.2 F.	96.1 F.	98.6 F.	—94 F.*	—94 F.	—94 F.	98.2 F.	98.2 F.

* The thermometer registered only 94 F

A foreign protein febrile reaction was induced by the injection of 125 million dead typhoid-paratyphoid bacilli intravenously. A chill occurred after one hour, and the mouth temperature rose from 99 to 101.6 F. With the onset of the chill, the pain in the arm was exaggerated. Following the chill, when the fever was at its height, the pain subsided, and the patient experienced the first comfortable night he had had for ten days. The temperatures of the skin showed a 2 degree rise in the right arm and a 3.2 degree rise in the left hand. The important information obtained from this study was the symptomatic relief afforded by the febrile reaction. After twenty-four hours, however, the pain returned in its original severity.

Second Operation (Dec. 9, 1928).—Sympathetic ganglionectomy, second dorsal; ramisection of first dorsal and stellate ganglion; procaine anesthesia.

The dorsal sympathetic chain was exposed according to the technic described by Adson.[1] The only variation made in the technic was the method of identifying the sympathetic trunk. This was done by isolating the second intercostal nerve, identifying the white ramus and following it down to its junction with the second thoracic ganglion. Once the ganglion was identified, it was a simple procedure to separate the chain from the pleura as one worked upward to the stellate ganglion. In this instance, the stellate ganglion was not removed, but the rami communicantes were severed. The chain was divided inferiorly between the second dorsal and third dorsal ganglion and superiorly just below the stellate ganglion. When the sympathetic trunk was severed and the ganglion removed, the patient, who was perfectly conscious under procaine anesthesia, insisted that he felt a warm wave pass downward over the arm and hand. The anesthesist reported an appreciable change in the warmth of the hand.

Skin temperature taken at the close of the operation showed a rise of 2.1 F. between all of the fingers of the right hand. Skin temperatures taken daily for two weeks following the operation showed that at no time did the temperature fall below 95.6 F., when formerly it was persistently below 94 F. The average temperature between the second and third fingers of the right hand was 97 F., and 98.4 F. of the left hand. A typical Horner's syndrome was produced on the side on which operation had been performed: absence of sweating on the right side of the face and neck and of the right arm with a corresponding contracted pupil and enophthalmos.

Course.—Symptomatic relief came promptly. Much of the time, the patient was completely free from pain; at other times, he complained of mild pain in the hand, particularly when he was nervous or upset in any way. Morphine withdrawal was started after the ganglionectomy. Two weeks after operation he required no morphine or other narcotics, except small doses of paraldehyde. The latter drug was used continuously in the hospital, after whisky had been withdrawn from his diet. Active and passive motion of the hand and arm was started after the second operation. After two weeks, he could perform feebly all motions of the forearm and hand. Pain in the left hand completely disappeared after the second operation. He was discharged from the hospital on December 23, greatly improved.

On Jan. 12, 1929, the patient was practically free from pain in his arm and hand. He was under treatment at this time for alcoholism. The temperature in the right hand by repeated observation was 97 F., and in the left hand 98.2 F. The fingers of the right hand were stiff and drawn in semiflexion. Dorsiflexion of the wrist could be performed weakly. The other motions of the arm and wrist were performed normally.

A communication from the patient's father on July 3, 1929, stated: "He has gained full use of his arm down to and including the wrist. The right arm is a little smaller than the left. The back of the hand and knuckles are inclined to sway down; the middle joints of the fingers are raised leaving the fingers in a cramped position. He has gained good use of his hand and arm as a whole in all directions; also he can use his wrist very well. He walks a great deal and is able to attend to business. He has no more pain."

COMMENT

Causalgia has been and continues to be one of the most troublesome of the "symptom complexes." When the main vessel to an extremity becomes occluded, the collateral supply may be sufficient to preclude the development of gangrene, yet insufficient to provide adequate blood for the normal metabolic processes of the tissues. The primary concern in every case, therefore, is directed toward improvement or increase in the collateral circulation. Why causalgia should develop in one case and not in another of the same nature remains a matter of speculation. Certainly, it has to do with the adequacy of the collateral vessels, and probably is directly related to the state of vasomotor control of these vessels. That the collateral vessels were capable of delivering sufficient blood to the arm for nearly normal metabolism was demonstrated in this case by removal of vasoconstrictor control. It was accomplished first, temporarily, by the foreign protein reaction and later, permanently, by the dorsal ganglionectomy. One may assume, therefore, that there was a normal or abnormal constricting mechanism reacting on the collateral vessels that was responsible for the pain and loss of function. It is unlikely that the symptoms could have been produced by pressure on the nerves, since neither the pain nor the hypesthesia followed any known anatomic patterns.

Another interesting feature in this case is the fact that during the periods of greatest pain in the involved arm and hand, the correspond-

ing member became equally painful. When the pain in the right arm was relieved, the left arm was free from symptoms. This phenomenon is characteristic of the pathologic condition known as allochiria, probably referred pain by a cerebral mechanism.

Leriche [2] recommended resection of a portion of the distal obliterated artery in cases of causalgia, his theory being that the same effect is produced as with periarterial sympathectomy. This procedure was done first in the aforementioned case, and there resulted complete relief from pain for three days only. Whether the excision of the distal obliterated artery or the ligation of the axillary vein was responsible for the temporary improvement in symptoms is problematic. Certainly, neither procedure produced any lasting beneficial effects.

CONCLUSIONS

One patient with ischemic causalgia of the arm, due to a gunshot wound of the second portion of the axillary artery, was successfully treated by dorsal sympathetic ganglionectomy. The improvement in the circulation and relief from pain in the extremity would seem to have been permanent.

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2. Leriche, R.: Nelson Loose Leaf Living Surgery, 1927, Thos. Nelson & Sons, vol. 3, p. 779.

MANIC-DEPRESSIVE PSYCHOSIS IN PRIVATE PRACTICE

LENGTH OF THE ATTACK AND LENGTH OF THE INTERVAL *

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Undoubtedly, hosts of manic-depressive patients are so mildly afflicted that hospitalization is not necessary. These patients are seen only in private practice, and they have not influenced descriptions of this disease because men who have written on this disorder worked in institutions for the insane, saw only institutional cases, and based their descriptions on these. Hospitalized patients are only those who are so malignantly afflicted that separation from society is necessary; hence, descriptions of manic-depressive psychosis as found in the literature deal only with the darkest aspects of the disease; the lighter forms, as seen in private practice, have no place in the literature. The situation is somewhat similar, for example, to what descriptions of diabetes would be if only hospital cases were described; almost every case of diabetes would then show acidosis, coma, gangrene and massive infection. But in diabetes, the milder, extramural forms have been given a place in the literature; not so in the case of manic-depressive psychosis.

In two previous communications [1] based on a study of 633 cases of manic-depressive psychosis in the private practice of Dr. Hugh T. Patrick, I reported some differences between patients observed in institutions and those seen in private practice. These reports were concerned with differences in sex distribution and age of onset of the first attack, and with the presence of many attacks which lasted from only a few hours to a few days. Further study of the same material disclosed other important differences between extramural and intramural cases; namely, in the length of the longer attacks and in the length of the intervals. These differences are the subject of this report.

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* Submitted for publication, Dec. 13, 1929.

* From the Department of Neurology, Northwestern University Medical School.

* Read at a meeting of the Chicago Neurological Society, Nov. 21, 1929.

1. Paskind, H. A.: Brief Attacks of Manic-Depressive Depression, Arch. Neurol & Psychiat. **22**:123 (July) 1929; Manic-Depressive Psychoses in Private Practice: Sex Distribution and Age Incidence of First Attacks, ibid. **23**:152 (Jan.) 1930.

LENGTH OF THE ATTACKS

Pilcz [2] and Bleuler [3] reported that the usual duration of attacks of manic-depressive psychosis is from six to twelve months; Ziehen,[4] from four to six months; Kraepelin,[5] from six to eight months; and Panse,[6] seven months. Swift [7] found that first attacks averaged seven months, and second attacks from eleven and one-half to fourteen months.

In my series there were 444 completed attacks. The distribution as regards duration is shown in chart 1. Of these, 50 per cent lasted

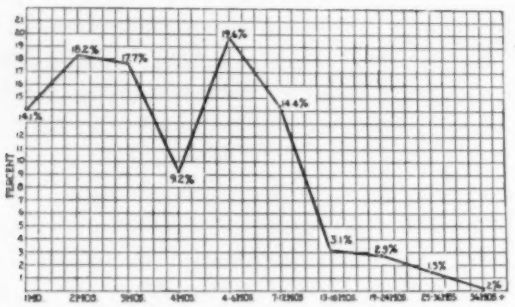

Chart 1.—Distribution of forty-four attacks according to duration.

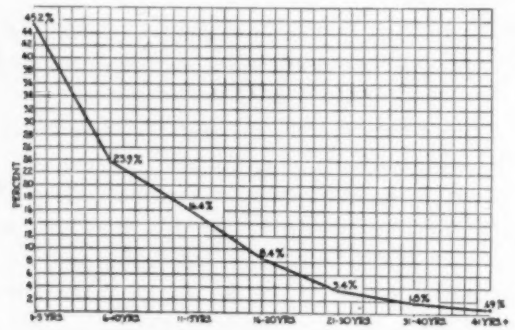

Chart 2.—Distribution of 438 intervals according to duration.

2. Pilcz, A.: Lehrbuch der speziellen Psychiatrie, Vienna, Franz Deuticke, 1926.

3. Bleuler, E.: Textbook of Psychiatry, translated by A. A. Brill, New York, The Macmillan Company, 1924.

4. Ziehen, T.: Psychiatrie, Leipzig, S. Hirzel, 1911.

5. Kraepelin, E.: Manic Depressive Insanity and Paranoia, translated by Mary Barclay, Edinburgh, E. & S. Livingstone, 1921.

6. Panse, F.: Untersuchungen über Verlauf und Prognose beim manisch-depressive Irresein, Monatschr. f. Psychiat. u. Neurol. **56**:15, 1924.

7. Swift, H. M.: Prognosis of Recurrent Insanity of the Manic-Depressive Type, Am. J. Insan. **64**:311 (Oct.) 1907.

three months or less; 59.2 per cent, four months or less, and 78.8 per cent, six months or less. Only 21.2 per cent lasted over six months. In other words, the great majority of attacks lasted six months or less, an observation markedly in contrast with that given in the literature.

The median value [8] for the length of the attack was four months. Having determined the median, I then determined if this median varied, and if so the conditions under which this occurred. The results are shown in table 1. A study of this table elicits some interesting facts.

TABLE 1.—*Variations in the Median Value for the Length of the Attacks*

	Number of Observations	Median Value, Months
Attacks in males	211	3
Attacks in females	233	4
Attacks, series	444	4
First attacks	248	4
Second attacks	112	3
Third or subsequent attacks	84	3
Onset of disorder, 10-20 years (all attacks)	103	3
Onset of disorder, 21-30 years (all attacks)	167	4
Onset of disorder, 31-40 years (all attacks)	111	4
Onset of disorder, 41-50 years (all attacks)	46	4
Onset of disorder, over 50 years (all attacks)	17	4
First attack between 10-20 years	46	3
First attack between 21-30 years	94	4
First attack between 31-40 years	66	4
First attack between 41-50 years	31	4
First attack over 50 years	11	4
Second attack between 10-20 years	25	3
Second attack between 21-30 years	45	3
Second attack between 31-40 years	28	4
Second attack over 40 years	14	3
Third or subsequent attacks, 10-20 years	39	3
Third or subsequent attacks, 21-30 years	25	2
Third or subsequent attacks, over 30 years	20	3
Attacks occurring between 10-20 years	58	3
Attacks occurring between 21-30 years	126	3
Attacks occurring between 31-40 years	130	4
Attacks occurring between 41-50 years	89	4
Attacks occurring over 50 years	41	4

Attacks in females are longer than those in males in the ratio of 4:3. The first attack is longer than the second or the third in the ratio of 4:3. The accepted conception is that as the disease progresses the attacks become longer (Kraepelin,[5] Henderson and Gillespie,[9] and Swift [7]). If the disorder begins between the ages of 10 and 20 the

8. The median is a standard statistical value. It is that value which in a series lies exactly in the middle. The median was used by Kraepelin who stated that it gives a more accurate view than the arithmetical average or mean, because the latter would be unduly influenced by abnormally long values.

9. Henderson, E. K., and Gillespie, R. D.: Text Book of Psychiatry, New York, Oxford University Press, 1927.

median for attacks in such patients is smaller than that in cases beginning at any subsequent period in the ratio of 3:4. The median for all attacks beginning in patients under 30 is shorter than for those after 30 in the ratio of 3:4. In other words, the attacks grow longer not in relation to their sequence but in relation to the age at which they occur.

LENGTH OF THE INTERVAL

Exact figures in terms of mean or median value for the length of the interval are sparse in the literature; most writers state that the interval may last for from a few days to many years. Dercum [10] stated that intervals of ten years are distinctly rare. Swift,[7] in forty-nine institutional patients in whom the first attack was a depression, found that the interval that followed averaged ten and one-third years, as against an average interval of six and one-half years in which the

TABLE 2.—*Differences Between Kraepelin's and the Present Series*

	Median First Interval	Median Second Interval	Median Third of Subsequent Intervals
Kraepelin	6	2.8	2
This series	8	5	4

	Intervals Lasting from			
	10 to 19 Yrs., per Cent	20 to 29 Yrs., per Cent	30 to 39 Yrs., per Cent	Over 40 Yrs., per Cent
Kraepelin	13.5	4.8	1.1	0.14
This series	27.8	5.7	1.6	0.92

first attack was manic, circular or mixed. In Swift's cases the average length of the first interval was greater after depression in men (twelve years) than in women (nine and one-half years). MacDonald [11] studied the length of the first intervals in 292 hospital cases; when the first attack was a depression the following interval averaged 10.6 years for men and 10.9 years for women, as against an average of 6.1 years and 6.5 years, respectively, when the first attack was excitement. Kraepelin's statistics [5] are more complete than any that I could find, and may be used as a basis for comparison. He found in states of depression that the median value for the first intervals was 6 years, for the second interval 2.8 years and for the third and subsequent intervals 2 years. In 703 intervals he found 13.5 per cent lasted from 10 to 19 years, 4.8 per cent from 20 to 29 years, 1.1 per cent from 30 to 39 years and 0.14 per cent over 40 years.

10. Dercum, F. X.: A Clinical Manual of Mental Diseases, Philadelphia, W. B. Saunders Company, 1913.

11. MacDonald, J. B.: Prognosis in Manic-Depressive Insanity, J. Nerv. & Ment. Dis. **47**:20, 1918.

In my series there were 438 completed intervals. The distribution as regards duration is shown in chart 2. The median value for the entire series was 7 years. The median for the first interval was 8 years, 261 cases; for the second interval, 5 years, 113 cases, and for the third or subsequent intervals, 4 years, 64 cases. In this series 27.8 per cent of the intervals lasted from 10 to 19 years; 5.7 per cent from 20 to 29 years; 1.6 per cent from 30 to 39 years, and 0.92 per cent over 40 years.

The differences between Kraepelin's series and the present one are shown in table 2.

TABLE 3.—*Variations in the Median Value for the Length of the Interval*

	Number of Observations	Median Value, Years
Intervals in males	219	7
Intervals in females	219	6
Intervals in the series	438	7
First intervals	261	8
Second intervals	113	5
Third or subsequent intervals	64	4
Onset at 10-20 years (all intervals)	91	7
Onset at 21-30 years (all intervals)	167	7
Onset at 31-40 years (all intervals)	118	7
Onset over 40 years (all intervals)	62	4
First interval between 10-20 years	52	9
First interval between 21-30 years	90	10
First interval between 31-40 years	69	8
First intervals over 40 years	50	4
Second interval between 10-20 years	26	6
Second interval between 21-30 years	50	6
Second interval between 31-40 years	37	3
All intervals commencing 10-20 years	60	7
All intervals commencing 21-30 years	135	7
All intervals commencing 31-40 years	123	7
All intervals commencing over 40 years	120	4

It is thus apparent that cases of manic-depressive psychosis in patients in private practice are characterized by longer intervals than institutional cases.

Further variations from the median for the length of the intervals are shown in table 3. Intervals in males are longer than those in females in the ratio of 7:6. When the onset of the disorder occurs at over 40 years, the median value for the interval is less than in those who have their onset before the age of 40 in the ratio of 4:7. The longest median value, ten years, is found in first intervals that commence between 10 and 20. All intervals that start after 40 are shorter than those that start before 40, in the ratio of 4:7.

CONCLUSIONS

The length of 444 attacks and 438 intervals of manic-depressive psychosis occurring in patients in private practice were studied and compared with similar values found in institutional cases as reported in the literature. The attacks occurring in extramural cases were found to be much shorter, and the intervals longer.

ABSTRACT OF DISCUSSION

DR. MEYER SOLOMON: Many men in private psychiatric practice have worked in state hospitals previously; those of us who have been in such hospitals know that we leave there with a pessimistic view. Many of us have this pessimistic view for many years. As I see it, one of the great handicaps of psychiatry at present is that many institutional men have not been able to throw off this pessimistic view. As a result of this, patients are practically chased away and do not come back. One of the bugbears has been and still is mental depression; our view has too often been that once a depression exists the patient is bound to have recurrences. Dr. Paskind's figures show that many of these patients have very short attacks and some of them very long intervals. Many have intervals of from ten to nineteen years between attacks of depression. The question comes up in these cases what shall one say to the patient and what to the family? I think many times that the family morale is destroyed, and if Dr. Paskind's paper does not do anything more than cheer one up a little and help one to encourage these patients and their families it will do much for those who carry pessimistic views on the subject.

DR. H. A. PASKIND: The longest interval noted in this series was four years. Whether or not there will be another attack I think depends on how long the patient lives.

CORRECTION

It is desired to call attention to an error in the communication by Drs. Penfield and Young, "The Nature of Von Recklinghausen's Disease and the Tumors Associated with It," which appeared in the February issue (ARCH. NEUROL. & PSYCHIAT. **23**:320, 1930). Throughout the text perineurial fibroblastoma is referred to as perineural fibroblastoma. The term perineurial was first used by Mallory to point out that these tumors arise from the perineurial connective tissue sheath. The authors regret that the alteration was not perceived in reading the proof, but they consider it essential that the nomenclature should not be further complicated by a new term. The same error was made in Penfield's discussion on page 301 of the same issue, in which perineurial should be substituted for perinueral fibroblastoma.

Clinical Notes

MULTIPLE TUBERCULOMAS AND INFARCTIONS OF THE BRAIN: REPORT OF A CASE*

ROBERT A. MOORE, M.D., CLEVELAND
Hanna Research Fellow in Pathology

Tuberculous arteritis of the cerebral arteries in tuberculous meningitis is not uncommon, but an associated thrombosis with infarction of the brain is of sufficient rarity to warrant this report.

REPORT OF CASE

History.—A colored girl, aged 5½, was admitted to the Babies' and Children's Hospital because of cough and fever of two weeks' duration. The history of birth was normal. Development and dentition were retarded. The past history was unimportant, except for measles one year before.

Examination.—The child was fairly well nourished and well developed, with a dry, scaly skin covered by a follicular papular eruption. The cervical lymph nodes were slightly enlarged. There was a purulent discharge from the nose. The percussion note over the right side of the chest was impaired, and there were numerous moist crepitant râles in this region. The heart was normal, except for a rough systolic murmur at the apex. There was a small umbilical hernia, 1.5 cm. in diameter. The liver extended 3 cm. below the costal border. Roentgenologic examination of the chest revealed a diffuse infiltration of both lungs with denser shadows at the right hilus. The spinal fluid was turbid, contained 73 cells per cubic millimeter and was negative for acid-fast bacilli. The tuberculin test was positive in dilutions of 1:100 and 1:1,000. The urine was normal. Examination of the blood revealed: hemoglobin, 70 per cent (Talquist); white cells, 13,100; polymorphonuclears, 62 per cent; lymphocytes, 30 per cent; eosinophils, 2 per cent; mononuclears, 6 per cent.

Course.—Pulmonary and cerebral symptoms became more marked, and death occurred three weeks after admission.

Clinical Diagnosis: The diagnosis was disseminated miliary tuberculosis and tuberculous meningitis.

Autopsy.—Autopsy, performed six hours after death, revealed acute miliary and conglomerate tuberculosis of both lungs with cavitation of the right apex, chronic adhesive pleuritis, caseous tuberculosis of the right peribronchial and peritracheal lymph nodes, miliary tuberculosis of the left peribronchial lymph nodes, tuberculous meningitis, multiple tuberculomas of the cerebrum and cerebellum, tuberculous arteritis with thrombosis of the cerebral arteries and infarction of the brain (right frontal lobe, right thalamus and left parietal lobe), miliary tuberculosis of the spleen, liver and kidneys, ulcerative tuberculosis of the ileum, tuberculous mesenteric lymphadenitis, cloudy swelling of the parenchymatous viscera and acute purulent otitis media on the right side.

* Submitted for publication, Jan. 6, 1930.

* From the Institute of Pathology, Western Reserve University, and the Babies' and Children's Hospital.

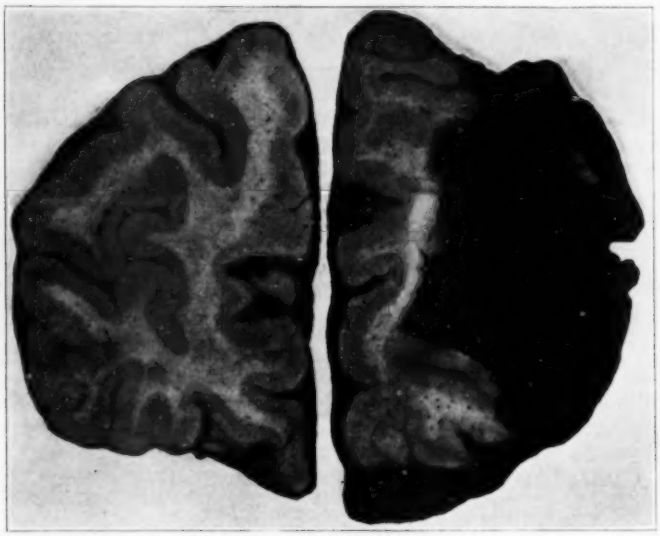

Fig. 1.—Coronal section through frontal lobes to show the area of infarction in the right middle and superior horizontal frontal convolutions.

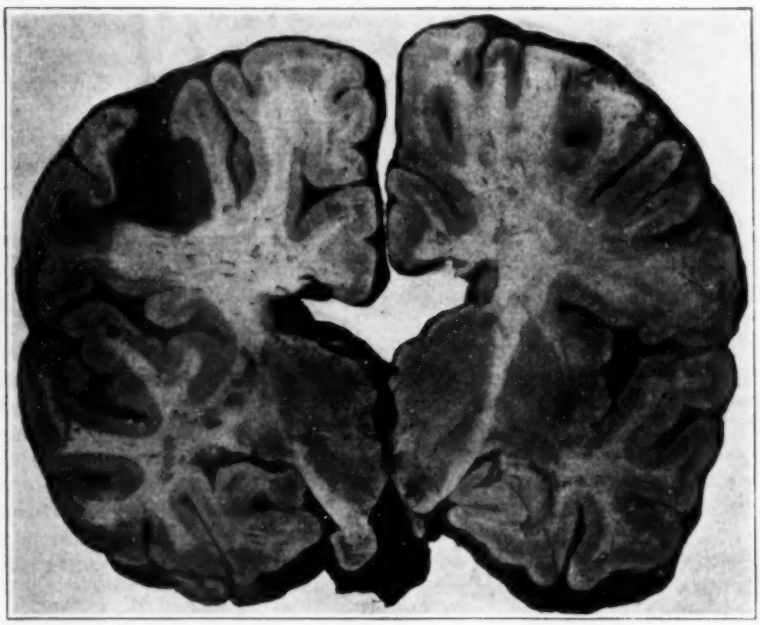

Fig. 2.—Coronal section of parietal lobes. Note the area of infarction in the left lobe and the small tuberculoma in the right lobe.

The detailed description will be limited to the brain. The scalp, calvarium and dura mater were normal. The pia-arachnoid was thickened throughout and contained numerous gray-yellow, firm, elevated nodules, from 1 to 2 mm. in diameter. The convolutions of the cerebrum were flat, and the sulci were narrow. The pia-arachnoid over the superior and middle horizontal frontal convolutions was dark red, and the arteries and veins in this area were dilated, firm and filled with dark reddish-gray, friable thrombi. There was a similar area, 1 cm. in diameter, in the left parietal lobe immediately posterior to the rolandic fissure. On section, these areas extended well into the brain substance (figs. 1 and 2) and were dark red and soft. In the right basal ganglia, there was an area, 3 by 3 by 1 cm., of similar appearance. In the cerebral hemispheres there were five small tuberculomas (fig. 2) varying from 3 to 8 mm. in diameter. There was a large tuberculoma, 1.5 cm. in diameter, in the right cerebellar hemisphere.

Microscopically, the brain substance in the hemorrhagic areas was edematous, and the nuclei of nerve and glia cells were pyknotic. The small blood vessels were filled with hyaline thrombi, and their walls were hyaline and infiltrated with polymorphonuclear leukocytes and lymphocytes. The Virchow-Robin spaces were filled with red blood cells. The larger vessels were filled with gray and mixed thrombi. The remainder of the brain was not unusual, except for slight edema and hyperemia. The tuberculous meningitis and tuberculomas had the usual histologic appearance.

COMMENT

Two points in this case deserve further consideration: the pathogenesis of the infarction and the occurrence of multiple tuberculomas. From the microscopic evidence there is little doubt but that the thrombosis is directly associated with a tuberculous inflammation of the arterial wall. Whether this is the sole etiologic agent it is difficult to state. In my experience, miliary tubercles in the wall of the cerebral arteries are common, but I have not observed ulceration of the intima.

The recent literature on the subject includes the papers of Ferris[1] and of van Wagenen.[2] Ferris found eight cases of tuberculoma in thirty-four instances of tuberculous meningitis, and in six the tuberculomas were multiple. Van Wagenen reported fourteen cases of tuberculoma and stated that they are most frequently solitary and located in the cerebellum. Of four cases in children seen in this laboratory, three were multiple. In two, the cerebellum was involved, but this was in association with cerebral lesions. This difference may be due in part to the source of the material. Van Wagenen's cases were from the surgical clinic of Cushing, while those of Ferris and this laboratory were observed in material from autopsies.

Small tuberculomas should not be confused with miliary tubercles of the brain substance. In practically every case of tuberculous meningitis, grayish-yellow soft areas, from 0.5 to 1 mm. in diameter, surrounded by a zone of hyperemia, are found throughout the brain substance. These represent early lesions, and it appears that the occurrence of gross tuberculomas depends in part on the severity of the associated meningitis and the survival of the patient for a sufficient time to allow full development of the lesions in the brain substance.

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1. Ferris, H. A.: Eight Cases of Tuberculoma of the Brain Found at Necropsy, J. A. M. A. **92**:1670 (May 18) 1929.

2. Van Wagenen, W. P.: Tuberculoma of the Brain. Its Incidence Among Intracranial Tumors and Its Surgical Aspects, Arch. Neurol. & Psychiat. **17**:57 (Jan.) 1927.

Obituary

GIOVANNI MINGAZZINI, M.D.
1859–1929

With the death of Giovanni Mingazzini, which occurred on Dec. 3, 1929, neurology has lost one of its leading representatives. Death found him holding the chair of nervous and mental diseases at the University of Rome, where for a quarter of a century he taught clinical neurology and psychiatry, and where he had been a living example of inexhaustible activity.

On his seventieth birthday, which he had only recently celebrated, he still was in the full extent of his activity, dividing his time between the most stimulating teaching and original investigation which he always carried with an ever-increasing enthusiasm.

Never satisfied with our actual knowledge, he was always avid for new facts, especially in the intricate field of neuro-anatomy and in the correlation between clinical manifestations and pathologic data. Because of his scientific tendencies, which might be called practical, Mingazzini has contributed largely to the progress of neurology in its various aspects: anatomy, physiology and pathology. The originality and completeness of his knowledge of anatomy are condensed in his textbook on clinical anatomy of the central nervous system. This book, which he unfortunately was not able to republish because of financial difficulties, was first published in 1913 and still stands as one of the fundamental works on clinical anatomy. Among the most interesting chapters may be mentioned the one on the development of the brain, with special reference to the brains of idiots. The chapter on the basal ganglia attracted, before Wilson's studies, the attention of investigators on the important functions of this region. Mingazzini always thought that lesions of the corpus striatum were followed by signs of motor deficiency. His conception, although not entirely accepted, finds some confirmation, especially in the study of the comparative development of function and structure in the various types of animals.

Another field in which Mingazzini has contributed extensively is that of aphasia, where he stood against Pierre Marie in defense of the

old conception of a motor and sensory aphasia with various well defined localized centers.

His studies on the cerebrocerebellar atrophies are well known; some of his pupils, inspired by his work, have themselves contributed toward a better understanding of the complicated anatomic correlations existing between the brain and the cerebellum. His work on the corpus callosum, which has attracted so many comments and quotations, represents another active field of his unceasing desire for clinicopathologic correla-

GIOVANNI MINGAZZINI, M.D.

tions. Among Mingazzini's last publications, the one dealing with the nucleus of the hypoglossus, which he investigated from the anatomic as well as from the experimental point of view, represents the most complete and reliable work on the subject that we possess.

An indefatigable worker himself, he developed numerous pupils, some of whom have already obtained considerable reputation.

Mingazzini was a member of the American Neurological Association and an honorary member of the American Medical Association.

Abstracts from Current Literature

MALARIA THERAPY OF GENERAL PARALYSIS AND SYPHILITIC INFECTIONS OF THE NERVOUS SYSTEM. WAGNER VON JAUREGG, Rev. neurol. **36**:889 (June) 1929.

This article is an epitome of von Jauregg's experience in regard to malaria therapy, a lecture before the tenth réunion neurologique internationale at Paris.

Two methods, the rational and the empiric, are offered in the treatment for general paralysis. The rational therapy has been followed by a series of disillusions, even with regard to the arsenical compounds. The empiric route was opened by the observation of unexpected remissions which followed intercurrent infectious diseases. In 1887, along with others, von Jauregg proposed the use of this type of treatment, and even suggested malaria as the ideal method, but on account of the dangers of provoking another disease in the patient he attempted to imitate such a disease by systematically applying microbic products or toxins. Although remissions were obtained, they were not satisfactory as to duration, and in 1917, he again went back to the proposition of 1887, and inoculated a number of paretic patients with tertian malaria. This method of treatment succeeded. Remissions became more frequent, more complete and more enduring than after any other method of treatment, and the treatment with malaria was taken up rapidly throughout the world.

There are certain questions about the treatment, however, that deserve to be discussed. In the first place, "What are the relations between malaria therapy and treatment by specific remedies?" Von Jauregg always combined treatment by tuberculin and analogous substances with specific treatment. In his opinion, "even if one did not attribute to the specific remedies the power of curing general paralysis, he would not have the right to say that they were without influence on this disease." And, also, in treating by malaria he has combined it from the beginning with a course of neoarsphenamine, later bringing the total dose to 5 Gm. There were authors who said that specific treatment was superfluous because complete and lasting remissions were observed without specific treatment, but one should always attempt to follow a course which yields the greatest profit for the patient. In comparing a series of cases of paretic patients who had been treated by malaria alone and another series who had been treated by malaria and neoarsphenamine he was able to demonstrate that the latter series had a larger number of complete remissions among the patients. On the other hand, there are partisans of specific treatment who say that the same results could be obtained by specific treatment as by malaria. It is not a question, however, of prestige between the use of malaria and of specific substances. Both methods are so far from giving 100 per cent good results in paresis that everything should be done to combat this disease; that is to say, malaria, which is doubtless the strongest of the nonspecific treatments, should always be combined with specific treatments.

"Which of these specific remedies should be preferred?" is also an open question. Von Jauregg has employed neoarsphenamine principally, but mercury, tryparsamide and other substances have been used.

The treatment with malaria should be administered as soon as the diagnosis is certain. All physicians who have employed this method agree that the results are much better if the process of the disease is caught in the early stages. In such early cases in his clinic, von Jauregg has secured complete remissions in two thirds of the patients and in fourteen cases in which lumbar puncture was done after two or three years, the reactions of eleven patients were completely negative.

In the face of these results it might be asked whether malaria should not be used in treating persons who are threatened with paresis. Such cases are to be found in latent syphilitic patients whose spinal fluid gives a positive reaction, and it is known that these cases are extremely rebellious to specific remedies.

The late Professor Kyrle has applied this method with such favorable results that it has been adopted by other syphilologists. It constitutes a true prophylaxis for paresis and tabes. "The ideal goal of syphilographers should be to guarantee syphilitic patients from the dangers of metasyphilis and not to leave to neurologists the burden of curing them."

The effects of the malaria are not all seen at once, and the improvement continues for a long time after the fever is terminated. Sometimes this latent interval amounts to months, and it sometimes happens that a paretic patient who is sent to a state hospital as incurable has returned to the clinic six months or more later on discharge as recovered. Similar reactions are seen after relapsing fever, but not after the use of tuberculin, vaccines, etc. Even more tardy in its appearance is the change in the serologic reactions. Even in the latent phases of syphilis the reactions of the person do not become negative immediately after malaria. In the paretic patient the latent period is even longer; sometimes it lasts two years or longer before the reactions become negative. This occurs also in patients who, after malaria therapy, have had no other treatment, either specific or nonspecific. This late change in the reactions has a prognostic value since the patients who show progressive improvement do not have relapses, while those whose reactions remain positive are always menaced by the danger of relapse. However, a negative reaction is valuable only in connection with clinical symptoms because in certain cases which have shown no clinical improvement the serologic reactions may be entirely negative. The opposite is also seen.

Finally, in cases of stationary paresis after treatment with malaria, with negative serology, there are patients who lose the slurring speech that has been a notable feature before treatment.

It is a question whether one ought to force the treatment by causing patients to undergo a large number of paroxysms. In many cases treatment has been followed by almost miraculous resurrection of the whole body, but the person should still have a period in which to accomplish this and should not be exhausted by too large a number of febrile attacks. From eight to ten attacks is the usual rule at Vienna, and the exhaustion from the height of the fever or from daily occurrence can be controlled by giving the patients a small dose of quinine.

It is preferable to stop the malaria after a moderate number of attacks and, if it is thought advisable to repeat the treatment after an interval of from one to two months. It cannot be denied that the attacks of malaria have killed a large number of patients, but this danger may be avoided by a number of procedures. Quotidian attacks frequently appear in the inoculated patients, sometimes immediately, or after a few tertian attacks. Quotidian attacks, which exhaust the patients, are brought about if large doses are used for injection, if the injections are made intravenously or if the blood group of the donor is the same as that of the recipient. In order to suppress daily attacks, small doses are given under the skin, or even into the skin, or a donor is chosen whose cells are agglutinated by the serum of the recipient. In other instances when the attacks come too frequently, a single dose of from 0.2 to 0.3 Gm. of quinine will stop the fever for several days, during which time the patient can reestablish himself; when the fever recurs the condition is apt to be less serious. In patients who apparently will not withstand the malaria, from two to four paroxysms may be given, followed by quinine, and during the interval of from four to six weeks injections of neoarsphenamine frequently give rise to the "resurrection" that von Jauregg speaks of. After this interval, a fresh inoculation is apt to be borne better by the patients, and from four to six paroxysms may be allowed. With these procedures the contraindications to malarial therapy have been reduced. Persons over 70 years of age have been treated. Tuberculosis has even undergone improvement during the malaria. In general, "one should follow the principle that it is better to interrupt the malaria and begin a new course after some time than to expose the patient to risk."

In treating patients for tabes, specific substances are often valuable and will stop the disease in its initial stages. The shooting pains are not necessarily an indication that the specific infection is active.

In treating patients for tabes, the absence of progress is the principal criterion. As long as there is no aggravation and the serology is negative there is no necessity for antisyphilitic treatment. If, however, progress is downward and treatment has had no effect, malaria may be used. Frequently, thus, the progress of the tabes is arrested even though at an advanced stage. In the advanced stages, however, with gross ataxia and incontinence, antisyphilitic treatment is equally as good as malaria.

The nonspecific methods of treatment in paresis are of three general types: the split protein products, the substances derived from microbes and the infectious fevers themselves.

Dr. Schilling studied the changes in the blood during the attacks and during convalescence. He found changes of exceptional value for regeneration. These are not present after the injection of other substances.

Von Jauregg is in agreement with most syphilographers who believe that therapeutic malaria has some action on syphilis in the secondary and tertiary stages, but not a particularly greater effect than other nonspecific treatment, and that the action of the specific remedies is superior in these cases if the patients are inoculated with malaria; in his experience malaria is not superior to specific remedies in syphilis of the vessels and mesoderm in the nervous system. The place in which malaria outstrips the other treatments, including both specific and nonspecific remedies, is in paresis, tabes and advanced latent syphilis. He maintains that the inoculated malaria has a special neurotropic action against the metasyphilitic infections. In the first place, the malaria is demonstrably better than the other methods clinically. In the second place, it has a direct action on the altered nerve tissue of paresis. This is shown by anatomic study of brains of patients who died during or soon after the malaria. In the third place, the chemical reactions in the cerebrospinal fluid, as shown by Donath and Heiling, are different from those obtained by other methods. Fourth, some paretic patients have shown a complete remission of the mental disease; yet, soon after the malaria, gummas of the skin and even syphilitic lesions of the blood vessels have been found. Von Jauregg expresses his belief that in some cases of paresis with favorable outcome, syphilis of the vascular system has become worse instead of improving. This applies particularly to the aorta. Finally, a positive Wassermann reaction is often much more persistent in the blood serum than in the spinal fluid.

Malaria cannot be used in all cases of paresis. There are patients in whom inoculation is ineffective, such as those who have developed an active immunity to the disease. A rare case of natural immunity is found. This immunity frequently disappears if intravenous doses are given at short intervals with larger quantities of blood, and two strains may be inoculated at the same time. Sometimes the malaria will stop after a few attacks; in such cases it may be revived by the injection of typhoid vaccine, but these procedures do not always work. Under such conditions one cannot be certain that the patient is not infected. Quite frequently plasmodia may be found in small numbers in the blood; even if not found by the microscope their existence may be proved by injecting the blood of such a patient into another person; active malaria frequently results. For this reason patients should not be discharged as immune without suppressing the latent infection by quinine.

When tertian malaria is not available other strains may be used. Kirschbaum has used quartan malaria, but this is encountered infrequently. Relapsing fever may be used. It is easily carried in the laboratory in white mice and encouraging results are reported with this method, but comparative experience has shown that the malaria treatment is superior; however, when malaria is not available relapsing fever may be used.

In closing, von Jauregg raises the question of reducing the incidence of paresis in the population. This is difficult because the neurologist and psychiatrist are not the physicians who see the patient first. However, it is well established that prophylaxis is more effective than treatment. This treatment should be begun in

the beginning and patients should not be allowed to leave without lumbar puncture to see if they are menaced by neurosyphilis. In such cases prophylactic treatment of the patient will prevent the development of these parasyphilitic disorders. "When this method is applied to syphilitics we shall less often be forced to submit paretics to malaria."

FREEMAN, Washington, D. C.

SOME ASPECTS OF THE PROBLEM OF THE EPILEPSIES. S. A. K. WILSON, Brit. M. J. **2**:745 (Oct. 26) 1929.

"The tendency to appear exact by disregarding the complexity of factors is the old failing of our medical history." Curnow's dictum is thus quoted by Wilson at the outset of his discussion of some of the problems of the epilepsies. He is under no delusion as to the complexities and intricacies of the subject. He characterizes its etiology as heterogeneous, its semeiology intermediate, its pathology dubious, its pathogenesis conjectured and its therapeutics empiric. He discusses the subject under six headings: clinical features, inheritance, experimental production of convulsions, occurrence of convulsions in pathologic states, the mechanism of the production of the epileptic seizure and the influence of other intercurrent affections on epileptic semeiology.

In summarizing the clinical features, Wilson stresses the difficulty arising from the clinical polymorphism of epileptic phenomena: motor, sensory, psychic and visceral variants. He divides the manifestations into an aura, the psychic component, the interruption of the stream of consciousness of varying levels, the motor content which varies from powerful repetitive muscular contractions at their wildest to the merest flicker of a finger, the sensory elements, visceral components of neurosympathetic origin, and the post-seizure manifestations.

He finds the factor of heredity persistently overrated, and the personal or constitutional factor underrated. It is time protest should be unitedly voiced by neurologists against a sinister prognosis to every case of epilepsy because of supposed inheritance. He summarizes the literature and assumes 20 per cent as the highest figure acceptable for direct hereditary influence. His own vast experience is productive of rare instances of epilepsy in siblings. It is impossible to draw any other conclusion than that direct heredity is of little moment in comparison to other inducing factors.

There are two main technical procedures in the experimental production of convulsions: (1) neural and (2) humoral. These may act separately or interrelatedly. He quotes the work of Dandy and Elman in their absinthe experiments with cats, and stresses the fact that cerebral injury lowers the convulsive threshold. The neural procedures elicit seizures due to the direct excitation of neural centers. The humoral procedures are defined as that component in the production of experimental epilepsy which consists of the alteration of the body fluids and biochemical constituents, either mechanical or in connection with exogenous or endogenous toxins. There is a table of mechanical, exogenous and endogenous humoral bodies from the work of Brock, Lennox and Cobb. Wilson mentions the three important observations: (1) that acidosis tends to inhibit, and alkalosis tends to augment convulsions; (2) increased oxygen tension in the tissues tends to inhibit while decreased tension tends to augment the convulsive state; (3) edema tends to increase while dehydration tends to diminish. His criticism is that modes of action are not satisfactorily determined. He quotes the work of Temple Fay as showing that the mechanical factor is at least as significant in numerous instances as any of chemical or biochemical nature.

If deductions as to determinants are to prove of value there must be evidence that these or some or other of these play a part in the production of epilepsy under pathologic circumstances. There are listed the organic (neural) states associated with epilepsy: tumors, infections, toxins, sclerosis and trauma. If one seeks a common factor for the development of convulsive states among these it will be hard to find. The humoral and vascular states associated with epilepsy are diseases of the blood vessels, disorders of the cerebral circulation (heart block, cerebral anemia, asphyxia, etc.), and disorders of the cerebrospinal fluid regulation.

An epileptic disorder is a disorder of the neuronic mechanism of the individual's neural network. True, it may exteriorize itself through the pyramidal system, but it may originate elsewhere. The crux of the pathogenic problem is: Is this neuronic disturbance (irritation or release) initiated in the neuronic mechanism itself or is the latter influenced by the humoral or vascular changes? Does one accompany or precede the other? Putting together the information garnered from the sections cited he summarizes by implying the existence of four determinants: (1) A mechanical determinant related to the amount and pressure of the cerebrospinal fluid. He quotes the work of Fay, Dandy and Foerster as to the relation established between the occurrence of increased pressure and the failure of fluid absorption. He accepts the work of Fay and Winkelman as sufficing to account for the delay in absorption of fluid, accumulation of fluid, back pressure, and consequent subarachnoid edema. Yet, Wilson says, given the pathologic circumstances explain the fits. (2) A vascular determinant: He cites the work of Francis Hare, in 1903, and points out the analogy of epilepsy to syncope. It is possible to harmonize the facts of clinical observation with experimental epilepsy, but "What is the proximate cause of the sudden initial vasoconstriction? When does it start?" The transient cerebral anemia is not sufficient to initiate convulsions. If this is the cause *per se*, then why is not every death bed the scene of convulsive seizures? How can the aura be explained? If the aura precedes the constriction, then what initiates the aura? How can one explain the state when the aura is not followed by convulsions? Is the existing condition neural or vascular? Wilson states his views as at variance with Sir William Gowers who says "The vasomotor theory is unneeded, unproved and inadequate." Yet the proof of the initiation of the whole sequence of events by a causal vasomotor constriction is lacking. (3) A humoral determinant: Physicochemical interchanges studied by Lennox and Cobb show that a fall of oxygen tension produces convulsions, and that the purpose of the convulsion is to counteract the oxygen deficiency. But this theory starts with a postulated constriction of the cerebral vessels, which is unexplained, of uncertain origin, and of dubious application to the various clinical symptoms which cannot be expelled from the epileptic category. (4) A neuronic determinant: The seizure is a neuronic derangement of neuronic derivation. The core of the situation lies in qualities of the neural mechanism exhibiting the discharge. It is impossible to find one single common factor for the totality of epileptic manifestations, unless the significance of some inherent nervous factor, some functional propensity, is allowed. However unsatisfactory the word "tendency" or "instability" may be, however useful it is in cloaking ignorance, I do not consider this a feeble conclusion; on the contrary, it is consonant with the facts of observation. The only trouble is that at present one cannot gauge "susceptibility" by reference to objective criteria. Nor, for that matter, can anyone estimate what is signified by susceptibility to infection or illness of any kind, unless by rather vague allusions to "immunity." But the question of immunity in epilepsy has never yet been seriously approached.

Hammond, in 1901, advocated malaria or erysipelas to cure epilepsy. Wilson quotes Bourneville and Bournaire (1882), Gowers, and Alden Turner to the effect that intercurrent infections, exanthems, typhoid, etc., ameliorated fits. Wilson has observed that measles and chickenpox have the most striking effects. Francis Hare says that pyrexia is significant and attributes the improvement to the general vascular relaxation and vasodilation. Whatever the explanation, it may yet turn out to be of importance from a pathogenic and therapeutic standpoint that epileptic manifestations are sometimes controlled by nature's own methods.

PALMER, Philadelphia.

CONDITIONS OF THE OPTIC NERVE CAUSED BY DISEASE OF THE SINUSES. EDGAR S. THOMSON, M.D., Arch. Otolaryng. **10**:248 (Sept.) 1929.

Sinus diseases are a well established cause of various conditions in the eye, especially of the optic nerve. Many cases of sinusitis show no intranasal symptoms. They are difficult to diagnose. Some people think that frankly purulent cases are

less likely to show lesions of the nerve than are latent cases. The author is unable to form an opinion on this question, but is inclined to think that in cases in which there is a free discharge the peculiar disease of the bone causing the condition of the eye is not so apt to exist. In the early investigation of this question, many cases in which every focus had been excluded went on to complete optic atrophy. Later, the author decided to operate in these cases "even when no nasal symptoms were manifest." The results were so good that the operations on the sinuses, which had at first been confined to cases of retrobulbar neuritis, were extended to cases of retinitis, choroiditis and even iritis. The results have been so good that he continues to operate in cases in which he finds no symptoms, many of these being latent cases in which the nasal symptoms could not be depended on. He operates in cases in which there is a strong probability of sinus disease, although often in these cases nothing is seen in the nose.

Three types of disturbance of the optic nerve occur as the result of disease of the sinuses:

1. Retrobulbar neuritis. "The nerve is slightly hazy and pale, with vessels either normal or somewhat diminished in size. Vision is markedly reduced, the blind spot is enlarged and the field soon becomes contracted. The color fields may be contracted or there may be a central color scotoma." This probably represents a plastic inflammation of the part of the nerve that lies nearest to the sphenoid and posterior ethmoid cells. Multiple sclerosis has not been the most common cause in the author's experience. In multiple sclerosis there is a progressive atrophy. In sinusitis there is a toxic neuritis which progresses to atrophy if not checked.

2. Plastic neuritis. "The nerve is reddened and covered with plastic exudates which usually extend irregularly into the retina. There are usually hemorrhages and perhaps an extensive chorioretinitis with large areas of retinal edema." Contractions of the field from the nerve alone do not occur early. If an operation is not performed, atrophy follows speedily.

In both 1 and 2 the disease is apt to be one-sided.

3. Sudden functional depression with no change in the appearance of the optic nerve. "It may be unilateral or bilateral. Central color scotoma is relatively common, while contraction of the visual field occurs only after the condition has existed for several days or perhaps weeks. The blind spot is usually enlarged. The pathology in this type is obscure." Long periods of depression — weeks and even months — may be followed by a return to normal in two or three days after the operation on the sinuses. Hysteria must be excluded. In these cases it is usual to find no local disturbance in the sinus and the rhinologist seems to operate on normal tissues. Nevertheless after complete operation the vision returns to normal with a rapidity that seems miraculous.

In latent cases, apparently the infection is not confined to the mucous membrane but spreads directly into the substance of the bone causing an osteitis of varying intensity but with little or no nasal discharge, with a tendency to hyperplasia. Sometimes the osteitis leads to caries and necrosis and a localized meningitis. In the vast majority of cases the posterior ethmoids and sphenoids are involved. The frontal sinus or the tonsils may be involved. The operation should be complete if one is uncertain of the extent of the area involved. According to MacKenty and Faulkner, a complete radical pansinus operation on the affected side is advised. Every ethmoid cell out to the orbital plate and up to the base plate is removed. The floor of the frontal sinus is opened and the entire anterior sphenoid wall is removed. The antrum is opened as widely as possible under the inferior turbinate. If the other side is evidently diseased it is similarly treated. One should never curet the sphenoid cavity. Removal of the tonsils is advised. Depletion helps, but the eye will not improve unless all diseased tissue is removed. The optic nerve begins to improve within forty-eight hours, especially in functional cases. Retrobulbar neuritis is slower, while plastic neuritis may require as long as several weeks to subside. The author emphasizes again "that this operation should be performed whether nasal symptoms exist or not. To wait for nasal symptoms in a serious type of case is to court disaster."

Complete recovery depends on the stage at which the operation is performed. In functional cases, considerable time may elapse and still the vision will return. However, with plastic forms great haste is necessary. As soon as the diagnosis is made the operation should be performed if destruction to the nerve tissue is to be avoided. A temporizing course may be allowable in the functional cases or in certain cases of iritis or choroiditis, but in retrobulbar neuritis or plastic neuritis it is not to be considered. The author says: "I have seen a number of cases in which suction or intranasal treatment was used instead of an operation and there was not one of these in which the nerve was not damaged to a greater or lesser degree."

In the diagnosis of functional cases, one must differentiate between sinusitis and hysteria. In plastic cases, diagnosis is made by exclusion through general tests (Wassermann, etc.) and examination of the nose. In the vast majority of cases optic neuritis from a constitutional cause is two-sided. In cases of multiple sclerosis, it is well to operate anyway as otherwise the outlook is hopeless and the multiple sclerosis may be toxic at any rate. In later cases in which the osteitis has run its course it is usually useless to operate, although some patients show surprising improvement.

The author gives an excellent review of the literature from 1926 to date. Sargnon and Colrat attribute some of the latent cases to reflexes from the sphenopalatine region. The consensus is for operation.

HUNTER, Philadelphia.

A GROUP OF BENIGN CHRONIC PSYCHOSES: PROLONGED MANIC EXCITEMENTS. F. I. WERTHAM, Am. J. Psychiat. **9**:17 (July) 1929.

This is a survey of older and current views on chronic manic states. Prolonged manic psychoses constitute a controversial field of psychiatry. The opinions held are based on a few recorded cases. Various states of dementia, with excitement, were designated as "chronic mania." Mendel contended that there was no such distinct disease picture. With the duration of an attack of more than eighteen months recoveries are rare exceptions. In the contrasting views regarding chronic mania there is no doubt that definitely schizophrenic conditions were included, as well as organic and other conditions in which prolonged or repeated excitements may occur. It was an axiom of the older psychiatry that after a certain number of years mental diseases become incurable, and later experience has crystallized into the view that recoveries after three years can be expected only in very exceptional cases. The literature shows a number of cases of "late recoveries," with varying opinions expressed, but Kreuser finally pointed out that they are not explained by accidental causes, shocks, trauma, etc., but are conditioned by the structure of the psychosis itself. Many of the cases reported were undoubtedly constitutional hypomanic personalities rather than definitely psychopathologic reactions.

Opinions varied also in regard to paranoia and its relation to chronic mania. Nitsche, in 1910, distinguished four groups of conditions of chronic mania type as: (1) original hypomania, (2) progressive manic constitution, (3) circular chronic hypomania and (4) constitutional excitement. Kirby called attention to the "transformation" of symptoms so that the condition had no similarity to the manic-depressive psychoses on the surface. Recent views regarding chronic mania still vary, but the majority of authors believe that acute conditions can but rarely become chronic and that the mixed states tend more to chronicity; the exact nature of these is little understood, though by some they are thought to have a relationship to dementia praecox in some cases reported.

The author reports seven cases of prolonged manic excitement, with a duration of from five to eleven years, in detail and discusses the symptoms diagnostically as affective (manic-depressive) psychoses presenting the essential symptoms and features of manic attacks, with a tendency to free and easy contact with the personal and social environment and frequently an emotional lability. Grandiose delusions were present in all cases; trends of delusions were demonstrated, and Wertham thinks that it would not be justifiable to regard these delusional features as foreign

to the manic reaction. The changes in the clinical picture during the course of the disease were marked in some cases, and with prolongation of the attack there were a more marked tendency to fluctuation, a reduction in overactivity and intellectual productivity, and a tendency to a certain monotony and automaticity and the appearance of delusional ideas. The recoveries seem to show that there is little danger of a permanent deteriorating change, probably owing to the fundamental failure of the manic state itself in that the patient is active and expansive; keeping his resources alive and in contact with whatever is available in his environment, and reaching to a great variety of things without any deep-lying conflict.

An attempt is made to formulate the conditions favorable to the occurrence of prolonged manic excitements, offering the existence of a manic constitutional factor, and "psychobiological rigidity," a character mode of reactivity of the whole personality of complex nature, as the two main prerequisites. Abraham is quoted as emphasizing the similarity of manic symptoms and normal behavior in childhood, and considering the manic attacks as a regression to childhood. Other recent opinions are offered and the deduction is made from them that there is a sweeping temporary change of behavior as if a whole barrier had been removed; a complete change of scene to childhood or to a different level in Schilder's conception. Three factors are suggested as assisting in bringing about "psychobiological rigidity": maturity of development, which is correlated with lack of elasticity, evidence of a characterologic rigidity in the premorbid personality and the existence of a pronounced reduction of intellectual equipment.

A statistical study of the frequency of prolonged manic excitements and of the duration and age at admission in 2,000 cases of first admissions to New York state hospitals from 1915 to 1927 is reported. The average duration of manic attacks is given as 241.7 days (34.6 weeks). The cases are shown to decline steadily in number as the duration increases up to one year and ten months, after which cases are very infrequent; charts are presented to show conclusively that prolonged manic attacks are very infrequent, only twelve women and two men having had attacks lasting for more than five years.

According to age at admission, the peak of the curve is between 20 and 25 years, the average 22 years. The condition is about equally frequent in men and women, and relatively very infrequent above 45 years. As to the duration of attacks of less than ninety days, there was a steady decline after the 20 to 30 years' period. It was also shown clearly in groups with a duration of from three to nine months that age is one of the most important factors in the development of chronic manic excitements.

The conclusion is offered from the study of the material presented and the cases recorded in the literature that it seems possible to single out a distinct group of prolonged manic excitements infrequently arising on a foundation of a manic constitution, with a tendency to recurrent acute manic attacks, reduction in the manic overactivity, with a tendency to fluctuation, absence of pronounced signs of deterioration and potential possibility of recovery from the chronic attack. On account of the long duration, paranoid outbursts, impulsiveness and contrariness, these cases are apt to be diagnosed as paranoid, schizophrenic or involutional psychoses of unfavorable type. Further investigation will lead to a closer understanding of the psychopathology of chronic states of excitement.

IRISH, Philadelphia.

OXYCEPHALY (TOWER SKULL): CASE REPORT WITH OTO-NEURO-OPHTHALMOLOGIC STUDIES. J.-A. BARRÉ, MLLE. WENGER and I. ALFANDARY, Rev. d'oto-neuro-opht. **7**:493 (July) 1929.

This most frequent congenital malformation of the skull is now oftener diagnosed, owing to the use of the roentgen rays. Formerly of almost exclusive interest to the ophthalmologist, cochlear and vestibular manifestations have attracted the attention of otologists, and now the authors show by this case report that this condition can produce multiple and various diseases of the central nervous system.

In 1921, an unmarried woman, aged 35, while in good health had severe pain in the left arm, followed by icterus and somnolence. She was cured in Baden-Baden and was well until the winter of 1923, when she developed monoplegia of the left arm, which was relieved by vaccines. From the winter of 1924, to the spring of 1927, she had severe right supra-orbital headaches which extended to the right occiput. Vertigo was present from the summer of 1926, when she experienced heaviness and stiffness in the right thigh. The lips felt as though coated with menthol; the tongue seemed heavy during speech, and tinnitus was present in the right ear. The family and previous history was not important. The speech, intelligence and gait of the patient were normal.

The first cranial nerve was normal; the second showed pseudopapillitis with marked hypermetropia (several months later, signs of bilateral optic atrophy). The third, fourth and sixth cranial nerves had good ocular motility. Touch, pain and heat were felt less on the right side of the face. The seventh and eighth nerves (cochlear) were normal. Spontaneous nystagmus was noted on looking in all directions, including vertical nystagmus downward. The patient past pointed from 4 to 5 cm. to the right and downward. In the Romberg test, the patient fell to the right, vestibular type of reaction. The caloric test of the right ear was made with water at 27 C.; there were normal nystagmus and deviation of the arms and body after the use of 25 cc. The caloric test of the left ear, with 50 cc. of water, gave a normal reaction. Turning test (ten turns in 20 seconds): To the right there was horizontal nystagmus, of small amplitude, lasting 30 seconds; to the left, nystagmus of greater amplitude, lasting 60 seconds. The galvanic test showed nystagmus with 10.5 milliamperes on both sides; examination of the ninth nerve showed the palate lower on the left and contracting better on this side; examination of the twelfth nerve showed hemiatrophy of the tongue on the right. The reflexes of the acromial and finger flexors were increased on the left. The Mendel-Bechterew sign was positive in the arm. The Babinski sign was positive on both sides. The abdominal reflexes, except the right inferior, were abolished.

Pain and thermic sensibility of the left leg and both sides of the trunk was slightly diminished.

The spinal fluid was normal; the Bordet-Wassermann test was negative.

To sum up, there were: conditions of varied intensity of the second, fifth, eighth (vestibular), ninth, eleventh and twelfth nerves on the right; bilateral pyramidal syndrome of the irritative type, more marked on the left, and a syringomyelic dissociation of sensibility also on the left.

The age of the patient, the transient character of the symptoms at first, as well as the irritative pyramidal and vestibular signs, suggested multiple sclerosis. These signs and symptoms, however, could be produced also by a lesion of the peripheral part of the bulb where are found the pyramidal fibers and the nuclei of the nerves. A roentgen examination of the head showed multiple deformities: the fronto-occipital line of the base formed a right angle; the occiput seemed soldered to the atlas; the posterior cerebral fossa was flattened, and the vault was increased in height. This led to an annular constriction of the foramen magnum, producing disturbance of the bulbopontile circulation. This hypothesis is rendered more probable by the fact that the conditions present indicated especially alterations in the peripheral zones of the bulb where the nuclei of the twelfth and ninth nerves, the vestibular centers, pathways of thermic and pain sensibilities and the motor pathways lie. Optic atrophy, a common sign in tower skull, was present but it was in the background.

The special points of the case reported are the relatively late appearance of optic atrophy, the multiple nervous conditions and the existence of vestibular (not optic) nystagmus.

It is questioned whether or not vestibular disturbances may not be more frequent than one thinks. Ruttin studied ten cases and found most often concomitant lesions of the second and eighth nerves, more rarely a lesion of the eighth (cochlear and vestibular) solely. He found either hypo-excitability or hyperexcitability of the semicircular canals, inexcitability of the verticals, or at

times inexcitability of all canals. Hyperexcitability was found especially in cases with parietal or occipital hyperostoses which he explains by a compression of the cerebellum. Hyperostosis in the occipital region was present in the authors' case but they think also that the pyramidal and sensory disturbances of the fifth, eighth, ninth and twelfth nerves point to a slow sclerotic process due to chronic circulatory disturbances. This would also explain the intermittence of the symptoms.

DENNIS, Colorado Springs, Colo.

THE NEED OF CONSOLIDATION OF PSYCHIATRIC THOUGHT BY A BROAD PROGRAM OF RESEARCH. SAMUEL T. ORTON, Am. J. Psychiat. **9**:1 (July) 1929.

Attention is called to the fact that structural reserve is beyond immediate needs. Nature is profligate with human brain, as elsewhere, and a cardinal step forward was made with the development of more effective communication in the acquisition of speech and, comparatively lately, of writing. Still, observations have always long preceded correct reasoning, requiring a series of master minds to produce fundamental assumptions of scientific thinking. Most complex of all scientific problems has always been the operation of man's mind. Its intrigue has caused observations to outstrip the capacity for interpretation, and disorders of the mind were interpreted in terms of magic or religion.

Pinel first saw mental disease as a medical problem and offered the beginning of the era of medicine in psychiatry. The work has been continued by analytic study of the psychoses, giving a framework for clinical entities. With the development in gross and microscopic pathology and bacteriology an understanding of the structural aberrations of the brain was gained in one fourth of the true psychoses.

As the yield became less prolific and more difficult to evaluate in this manner, interests turned toward study of environmental and social influences, with contributions from psychogenic philosophies, till now the major attitude of psychiatry is focused in this restricted path. The work in psychiatry is mainly an estimate of problem behavior and the attempt to control it, similar to the experience of everyone; hence, many laymen feel prepared to pass judgment on technical problems and there is need for stronger security to establish the challenged tenets. There has been a tendency to seize new theories and unproved methods and to exploit them to the neglect of accurate records and painstaking observation. The application of the principles of psychiatry in the fields of mental hygiene and child guidance are proper, but there is a tendency to lessen the contact with medicine. Much of this work is not medical, but there is a need to establish the value of the medical point of view and require medical training for the leaders, for there is encroachment from all sides.

Psychologists offered psychometric testing, but the psychologist's approach is the obverse of that of medicine, in that the effort is made to establish a norm, while medicine's ambition has been to find the causes of the deviations. Collaboration is desirable, but not replacement or competition. There is a tendency for untrained or badly trained psychologists, social workers and others to trespass on psychiatric fields, even to the establishment of sociologic clinics offering service and advice in problems of social adjustment without a psychiatrist's direction. Errors and dangers in treatment are obvious when no medically trained person is associated. A definite standard is needed for psychiatric teachers and practitioners because some present procedures are a real menace to the profession and to the public. There is room for specialization within psychiatry as, for example, in contact with law which is stable and conservative and offers a contrast to more progressive psychiatry.

The problem today is to correct the evaluation of intrinsic and extrinsic factors in etiology, which requires more research in the physiology of the brain, and the attempts to correlate them with psychopathologic material by a broad approach. The suggestion is offered that the instincts and emotions could be approached biologically, also by genetic studies of emotional constitution. Another problem for study is the anatomic substrate of the emotional responses and correlation with stages of maturation of the brain.

An organic background of psychoses is established in senile dementia, excluding vascular types; the causes for differential ageing, selective senility and cacogenetic development remain unsolved, as well as the problems of direct anatomic investigation of the cortical layers. There is lack of knowledge regarding the structural background of amentia. The brain passes through several critical developmental periods. Studies in dementia praecox have not shown causative microscopic changes, but do not exclude structural factors entirely. The normal pathways in the cortex are not known in detail — synaptic interconnections are not known. Structural changes are not all the organic possibilities; intricate chemical relations are not understood. The phenomenon of resurgence by defect may explain much. A too thorough acceptance of evidence now available tends to limit research.

The presentation is a plea for the maintenance of a broad and critical point of view in psychiatry: "All the structures of an organism are the product of a progressive evolution and all attributes of an organism are dependent upon the activities of its structures." Research should study the origin and meanings of the structures of the brain and should aim at correlation of function with structure. An enviable position in the program of human improvement lies open to psychiatry, with the establishment of researches on a sufficiently broad basis.

IRISH, Philadelphia.

NEUROGENIC AND PSYCHOGENIC DISORDERS OF THE ALIMENTARY CANAL. JOHN L. KANTOR, J. Nerv. & Ment. Dis. **70**:28 and 179 (July-Aug.) 1929.

The disturbance of nervous control over the digestive apparatus has long been understood as a cause of dyspepsia. The intrinsic nerve apparatus of the alimentary canal, consisting of the plexuses of Meissner and Auerbach in the intestinal wall, is reviewed. These are considered more as coordinating than as initiating in their effect. There is the exciting element or the parasympathetic or vagus opposed by the inhibiting or sympathetic, and these elements constitute the extrinsic nerve apparatus with three levels of neurons: (1) the suprasegmental, arising in the diencephalon in the floor of the third ventricle; (2) the segmental visceral system of the brain and spinal cord; (3) originating in the ganglia or plexuses, either remote or adjacent to the cord.

The hypothalamic or diencephalic center serves as coordinator of the lower segments of the entire visceral nervous system. A reflex of the first level is illustrated by peristaltic response to a bolus of food; a spinal segmental reflex is shown by paresthesias of the head which occur when the pelvic colon is overloaded; the highest segmented reflex is exemplified in the responses of the alimentary tract to emotions. The rôle of the cortex is never excitatory, but only inhibitory to visceral reflexes of the lower orders. In infancy and unconscious states the lower centers predominate, while as development proceeds the higher centers make possible the establishment of voluntary control.

In neurotic patients a condition of constitutional nervous instability has been assumed in which hypersensitive nerve pathways result in the magnification of normal centripetal or centrifugal impulses. The exact nature of this debility requires more neuro-anatomic and pathologic investigation for its understanding. Fatigue, alcohol, nicotine and caffeine all affect the visceral nervous system, and the dependence of the autonomic nervous stability on internal secretory balance has been one of the dogmas of modern endocrinology. However, there is a sad lack of precise pathologic data on which to base these assumptions. Leupold studied twenty-three cases of tuberculous enteritis and found that in the seven which showed diarrhea the plexuses of Auerbach were involved by perineural and periganglionic round cell infiltration. Generalized neurofibromatosis has been found to involve occasionally the nerve endings in the digestive organs. Disorders of the digestion founded on disturbances of the ganglionic arc are not easily related to precise lesions because of the poorly understood anatomy of these ganglia. On the basis of Langley's experiments with nicotine Hurst explains the relaxing effect of moderate smoking on the gastro-intestinal tract with the phenomena of preliminary stimulation and later paralysis of the ganglionic synapses. Laignel-

Lavastine associates shock in peritonitis with paralysis of the solar plexus. Two personal cases showing painful abdominal seizures are offered by the author as suggesting some lesion of the solar plexus. Emminghaus reported two cases of chronic constipation with pathologic changes in the splanchnic nerve. Leb studied a case of gastric atony with scars involving the vagus nerve, but opposite effects have been described by Keiser with the same cause. Thus it is hard to get the causal relationships in involvements of the second neuron level. In most cases of myelitis it is difficult to distinguish the segmental from the suprasegmental involvement. Neural ileus has been observed in high cervical and high thoracic transverse myelitis. Digestive disturbances, hypo-acidity and hyperacidity of the stomach, vomiting, abdominal distention and obstinate constipation have all been described in epidemic encephalitis, which so often involves the sympathetic center in the diencephalon. Reichard has ascribed the emaciation of paresis to a specific degeneration of the vegetative trophic centers in the hypothalmus.

When one turns to the cerebral cortex one finds, according to some authors, evidence for centers possessing control of digestion. Psyche and digestion are so reciprocal in their relations that it is often hopeless to try to determine the relative etiologic value of their respective components. Anorexia, globus, nausea, vomiting, belching, flatulence and diarrhea have all been reported in the psychoneuroses, but many of these have been found related to organic lesions such as ulcer, colitis or gallstones. Many psychic disorders of digestion, habits and peculiarities are founded on early conditioned reflexes.

HART, New York.

A CASE OF MARKED BONY OBTURATION OF THE FORAMEN MAGNUM BY A MOBILIZED AND DEFORMED DENTATE PROCESS WITH THE PRODUCTION OF A CLINICAL PICTURE RESEMBLING SYRINGOMYELIA. E. J. MEIER, Schweiz. Arch. f. Neurol. u. Psychiat. **24**:303, 1929.

Meier reports the case of a woman, aged 79, who since the age of 30 had suffered a gradually increasing deformity of the hands and feet, and since the age of 69 had developed evidence of involvement of the central nervous system. The disease involving the joints began in the fourth digit of the right hand, and then appeared in the ball of the right foot; subsequently, the knees and the elbows became swollen and painful. There was no fever. Gradually, a marked deformity of all joints of the hands and feet appeared. The deformity of the hands was such that the fingers appeared to dangle from the metacarpophalangeal articulations, the heads of the metacarpal bones over-riding the proximal ends of the phalanges. All movements of the head were limited; the spine showed a scoliosis in the dorsal region. The patient complained of attacks of dizziness. She could knit and sew almost to the last.

There was nystagmus on looking toward either side. The fingers were markedly cyanotic. The upper extremities were very atrophic, particularly the left. Fibrillary tremors were noticed in both deltoid and pectoral muscles. Sensibility of pain and temperature was impaired; this impairment was particularly marked over the posterior aspect of the left forearm and the anterior aspect of the left leg. These qualities of sensation were slightly impaired over the upper arm and anterior portion of the thorax on the left side, and over the anterior surface of the right leg. The abdominal reflexes were absent; the tendon reflexes were increased, the right patellar more so than the left; Babinski's sign was positive. Roentgenograms disclosed luxations of the metacarpophalangeal and metatarsophalangeal joints, marked rarefaction of the cortex of the bone and some proliferation. The diagnosis of the neurologic lesion was syringomyelia.

At necropsy, the body was very emaciated; a decubitus was present over the right buttock. The foramen magnum was almost entirely occluded by a hard bony prominence which left a crescentic slit at the left dorsolateral aspect of the spinal canal through which the spinal cord passed. Roentgenograms taken at this time showed a deformed and dislocated odontoid process; it was not known whether these changes could have been demonstrated during life. Meier remarked that examination should have been made, particularly in view of the limited movements

of the neck and severe pain over the occipital region of which the patient had complained. It was obvious that the skull had gradually slipped forward on the atlas, and that the odontoid process had compressed the cord.

Microscopic sections of the tumor showed a friable, spongy odontoid process. The transverse ligament had undergone a bony, cartilaginous change; this had freed the odontoid process and had led to dislocation of the skull on the spinal column. The left olive was slightly compressed. The maximum compression of the cord had taken place immediately under the crossing of the pyramidal tracts. The right anterior column and the lateral column showed a reduction in the number of fibers. There was less diminution in the number of fibers in the remainder of the cord, with the exception of the right tract of Goll, where the loss of fibers was quite obvious. Secondary degeneration was noted.

Meier was unable to find the report of a similar case in the literature, and so far as he is able to say this case is unique. In his opinion, the patient suffered primarily from a disease of the joints and ligaments, including the transverse ligament which serves to fix the odontoid process. This had resulted in a forward dislocation of the skull on the atlas with consequent compression of the spinal cord.

In 1924, Schulthess published a case report in which he described tuberculosis of the atlas and axis which had resulted in a forward dislocation of the skull. A paresis of the left half of the tongue had been the outstanding neurologic sign.

WOLTMAN, Rochester, Minn.

OLFACTORY GROOVE MENINGIOMAS AND MENINGIOMAS IN GENERAL. A. BOSTROEM and H. SPATZ, Nervenarzt **2**:505 (Sept. 15) 1929.

In this article attention is called to the marked advances in neurosurgery in America, as compared to Germany. The monograph of Cushing and Bailey is cited as indicating not only the surgical progress but the strides that have been made in histopathology. The subject of the article is a discussion of meningiomas, with special reference to tumors of the olfactory groove. Cushing's monograph, in which he discusses seventeen meningiomas of the basal frontal area, is reviewed.

Meningiomas are slowly growing tumors. They do not infiltrate the brain substance though, due to their size, they may so compress the brain substance as to give the appearance of extension. Because of their encapsulated nature they are a group of operable tumors. In spite of the large size of these tumors, they may exist for a long time without the usual cardinal signs of tumor of the brain. This is especially true in frontal lobe meningiomas. Meningiomas rarely have regressive changes. Calcification occurs occasionally and whenever a roentgenogram shows calcification the possibility of a meningioma must be considered. These tumors are among the most common. Cushing found in 751 tumors of the brain, 85 meningiomas, or 11.3 per cent. In 1929, Cushing increased this percentage to 19. The authors, in a verified series of 60 tumors, found 40 per cent to be meningiomas. This high figure is partly the result of including several symptomless meningiomas which were found accidentally at postmortem examination. Meningiomas of the cord and of the tuberculum sellae are much more apt to give early symptoms, due to the adjacent important structures.

In 1922, Cushing divided meningiomas as follows: (1) spinal, (2) cranial nerve, (3) suprasellar, (4) olfactory, (5) sphenoidal, (6) temporofrontal, (7) meningioma of the convexity, (8) parasagittal, (9) falx and (10) meningioma of the sinus transversus and sigmoid.

In this article the writers confine themselves to group 4. The olfactory meningiomas have their origin near the lamina cribrossa, that is, near the middle of the anterior fossa. In reporting their conclusions the authors state that they completed their work prior to their knowledge of Cushing's monograph. Their first two cases belonged to symptomless meningiomas which were discovered at postmortem examination. The next case was incorrectly diagnosed as taboparesis; at postmortem examination, a large olfactory groove tumor was found. The fourth case was correctly diagnosed, as the authors had by that time become alert to the olfactory groove syndrome. From the author's cases, a triad of localizing symptoms may be postulated: (1) loss of smell, (2) visual failure, (3) psychic

changes. This triad is of slow development, usually covering a period of several years. Symptoms of increased intracranial pressure are uncommon in spite of the large size that these tumors may attain. The roentgenogram may show a shadow, as occasionally these tumors are calcified. In the differential diagnosis, attention is called to the occurrence of glioma in the frontal basal area. As a rule these tumors are much more rapid in their development and should rarely be confused. Pituitary tumors with their endocrine symptomatology should cause no difficulty, especially if a careful history of the course of the symptoms is obtained. Meningiomas of the sellar region may cause difficulty in diagnosis but as a rule visual disturbance appears comparatively early, while anosmia and mental changes appear rather late. It is also important that paresis be thought of, as frequently the psychic symptoms are so marked as to cause confusion. In conclusion the authors discuss the surgical technic as outlined by Cushing.

MOERSCH, Rochester, Minn.

STUDIES OF THE CEREBRAL CIRCULATION BY PHOTOMICROGRAPHY. RISER and SOREL, Rev. d'oto-neuro-opht. **7**:485 (July) 1929.

This article is a description of an ingenious and painstaking method of observation of the cerebral vessels, by stereoscopy and photomicrography. The authors first show plethysmographic records of arterial tension and cerebral volume after intravenous injection of (1) acetylcholine, 5 mg., (2) of epinephrine 0.1 mg. and (3) the inhalation of carbon dioxide (1 liter in one second). In the first case, both arterial tension and cerebral volume are simultaneously diminished; in the second, there is immediate increase in arterial tension and cerebral volume; in the third, the arterial tension is not changed but there is diminution of cerebral volume at the same time that the respiratory movements are increased in frequency and amplitude. (It is difficult to say whether this is due to vasoconstriction or is purely a passive diminution of cerebral volume secondary to the increased respirations.)

The cerebral vessels were then directly observed and photographed while repeating the described experiments with the following results: (1) After injection of acetylcholine (which produces a fall of arterial pressure and diminution of the cerebral volume) the photographs of the cerebral vessels show that the caliber does not vary. Hence, this phenomenon is not due to spasm of the cerebral arteries. It is due to general vascular hypotension and slowing of the systoles. (2) After epinephrine injection (producing a marked increase in arterial pressure and in cerebral volume) the photographs of the cerebral vessels show an immediate and considerable vasodilatation, not secondary to an arterial spasm, and at the same time there is marked arterial pulsation. This is the epinephrine paradox, showing the very special character of the cerebral circulation. The brain behaves like an extremely dilatable sponge at the moment of peripheral and abdominal vasoconstriction. They ask whether this is due to the vasodilators proper or is a purely passive distention. The latter is more plausible. (3) The plethysmograph showed, during inhalation of carbon dioxide, a clear but slight diminution of cerebral volume accompanied by increased respiratory movements. The photographs show that this is not due to vascular spasm. On the contrary, there is an immediate but slight dilatation in three fourths of the cases. This vasodilatation is not due to amplified respiration because it is observed when the phrenic nerves have been paralyzed and respiration is artificial. How can the contradictory facts of vasodilatation and diminution of cerebral volume be reconciled? The authors think that the slight arterial dilatation produced by carbon dioxide is immediately compensated for by the call of venous blood produced in the chest during the forced and rapid respirations which follow inhalation of carbonic acid gas.

These experiments show: (*a*) the ease with which the brain can be passively engorged or emptied of blood, and (*b*) that registration of the cerebral volume and pulse is not sufficient in the study of cerebral circulation. It is necessary to complete it by direct streoscopic observation and photomicrography. The details of the method are described.

DENNIS, Colorado Springs, Colo.

THE RELATION OF MUSCULAR TONUS AND THE PATELLAR REFLEX TO MENTAL WORK. F. L. GOLLA and S. ANTONOVITCH, J. Ment. Sc. **75**:234 (April) 1929.

Muscle tonus in the extensors of the knee and wrist was recorded by means of attachments to the toe cap of the shoe or to the middle knuckle of the pendant foot or hand, respectively. For mental work, the person added a series of columns of figures, which were read silently or aloud (establishing a time relation by pressing the button of an electric contact marker at the end of each column), or he performed certain muscular exercises that required close attention. The records that were secured showed invariably the same type of response: an immediate rise of tonus at the inception of the work; maintenance at a maximum for a brief period, and then a gradual return to the original level even though the work was still in progress. The tonus curve reached the original level long before signs of fatigue could be traced, often while there were signs even of increased efficiency, and no change occurred, either in the form of prolongation of the maximum or in the alteration of the rate of subsidence, when the work was made progressively more difficult. The increase of tonus preceded the actual beginning of the work and reached its maximum in from ten to forty seconds. The maximum tonus that was reached bore no distinct relation to the difficulty of the work that was performed, but the duration of the hypertonus was sensibly shortened by fatigue. Records in a case of tabes presented no evidence of a rise of tonus during mental work; in a case of pyramidal spasticity the height of the increase was raised but the duration was not prolonged.

Studies on the knee jerk during similar mental work gave a curve similar in all respects to that of the tonus. The knee jerk at once ascends to a maximum and then descends to a normal level despite the continuance of the work at the original or even at an increased efficiency. During these experiments, however, great variability in the individual responses to identical successive stimuli was observed; one response might even be as much as ten times that to the preceding stimulus. Such variations were noted only when the responses were submaximal and occurred equally, under these conditions, during an increased response under mental effort. If the knee jerk was rendered maximal, either by using maximal stimuli or by intense effort on the part of the subject, the variations almost entirely disappeared. No correlation was observed between the spontaneous variations of the knee jerk and the muscle tonus when the subject was at rest. The authors therefore distinguish two types of variation in the knee jerk: one that depends on mental effort and the effects of affective stimuli, and the other a random individual fluctuation. The latter type was observed when the person was under deep anesthesia and was also found to be bilateral. The authors suggest that these random variations result from "endogenous fluctuations of excitability" of isolated centers in the cord and are phenomena similar to the spontaneous muscular twitchings observed in the spinal animal.

SINGER, Chicago.

MENINGIOMAS OF THE ANTERIOR CHIASMAL ANGLE. R. GUTTMANN and H. SPATZ, Nervenarzt **2**:581 (Oct. 15) 1929.

In this article the authors adopt a rather unwieldy title in place of the term used by Cushing, meningiomas of the tuberculum sellae. In a previous article, Bostroem and Spatz reviewed their work on meningiomas, discussing in detail group 4 as classified by Cushing. In this work they take up group 3, or the so-called suprasellar meningiomas. They report three cases.

Case 1 was one in which the tumor was accidentally found post mortem in a patient who died of pseudobulbar palsy. The tumor was so small that it produced no symptoms. From an anatomic study it was found that the tumor had its origin at a point anterior to the tuberculum sellae; for this reason the authors use the term, meningiomas of the anterior chiasmal angle.

Case 2 was that of a woman, aged 40, who had noted failure of vision of the right eye, six years previously. Five years after the onset of the trouble, vision

began to fail in the left eye and a diagnosis of pituitary tumor was made. Postmortem examination disclosed, instead of a pituitary tumor, a meningioma of the anterior chiasmal angle.

Case 3 was of a woman, aged 42, who had noted loss of vision in the right eye, seven years previously. A year later, the left eye became involved. By September, 1928, the patient was totally blind. She showed gradual mental deterioration and died following an exploration. At autopsy a large meningioma was found; the point of origin, while not clearly defined, appeared to be in the region of the tuberculum sellae.

These three cases represent fairly clearly the stages of development in meningiomas of the chiasmal angle. They are chiefly distinguished from the olfactory groove meningiomas in that they early produce visual defects, and only later symptoms in the adjacent area, especially of a pituitary character, which would tend to change the picture.

Cushing postulates four points on which a diagnosis of meningioma of this region may be made: (1) the occurrence of the syndrome in middle life (from 40 to 50 years of age); (2) visual disturbance, especially of a bitemporal hemianopic type; (3) a primary optic atrophy shown in the fundi, and (4) absence of sella changes and of pituitary signs, except in the late stages.

In discussing the differential diagnosis the authors first take up pituitary tumors, Rathke pouch cysts and olfactory groove tumors. They mention the possibilities of parasellar meningiomas, and refer to Cushing's classification which includes meningiomas of the chiasm, meningitis and chronic arachnitis of the basal cistern, secondary hydrocephalus and aneurysms of this area. In conclusion the authors state that it is apparent that meningiomas of the anterior chiasmal angle are not uncommon, as Holmes and Sargent reported ten cases, and Cushing fifteen cases. They take up briefly the surgical aspect of the problem.

MOERSCH, Rochester, Minn.

ON THE EPIDEMIC OF DISSEMINATED INFLAMMATION OF THE NERVOUS SYSTEM IN POLAND IN 1928. EDWARD FLATAU, Encéphale **24**:619 (July-Aug.) 1929.

During 1928, the author observed cases which were impressive because of the singularity of the symptoms. The onset was sudden, sometimes with pains of peculiar localization or bizarre hyperesthesias, sometimes with pareses or paralyses. The symptoms included cranial nerve disturbances such as facial palsy; unilateral visual alterations (haziness and blurring); occasional involvement of the sphincters; cerebral symptoms of convulsion or speech disorder; a normal temperature or but slight elevation and then only for a short time, and usually little disturbance of sleep. All symptoms were mild and often fugacious; they did not necessitate confinement to bed. The total series comprised about twenty-five cases, of which seventeen are summarized in the paper; two fatalities occurred. These all constituted cases of an epidemic of local proportions that were seen by the writer in his private and consulting practice. The majority of the patients were children between the ages of 11 and 13 or young adults; one patient, aged 67, is listed.

The histopathologic study in one case showed infiltration of the central ganglia, of the spinal cord, and about the roots of some of the peripheral nerves. A neuroglial reaction was manifest, with a tendency to the accumulation of these cells about the vessels; neuronophagia was rarely observed. The meninges were the site of extensive infiltrations, especially about the pons.

Then follows a comprehensive review of the case studies in the literature of those conditions which fall into the three categories of endemic encephalitides per se; of encephalitides and myelo-encephalitides complicating acute infections, and of so-called sclérose en plaque. Basing his statements on all these studies, the author has arrived at the conclusion that the appearance of small foci of epidemic or endemic diseases approximating a disseminated myelo-encephalitis is probably to be considered as having a relationship to the large epidemic of epidemic encephalitis. It is possible, with certain reservations, that one would be obliged

to classify in the same group the nervous complications that are so frequently observed in recent years in the course of the infections of variola, varicella and rubeola. The augmentation of the number of acute and abortive cases of sclérose en plaque imposes also the hypothesis of the influence of the major epidemic. It is, however, impossible to solve as yet the question as to whether the human organism's resistance was lowered under the action of the epidemic or whether the same virus was responsible for the pathologic condition in all these groups.

ANDERSON, Los Angeles.

THE SO-CALLED SMALL ROUND CELL INFILTRATIONS: II. SYPHILIS OF THE CENTRAL NERVOUS SYSTEM. N. A. MICHELS and J. H. GLOBUS, Arch. Path. **8**:371 (Sept.) 1929.

This is a continuation of work by the authors on round cell infiltration. Previously they had demonstrated that the vast majority of infiltrating elements in the adventitial spaces are emigrated lymphocytes, large mononuclears and homoplastic derivatives of the emigrated cells. In this article they state their belief that in syphilis of the nervous system the vast majority of infiltration elements in the adventitial spaces are emigrated lymphocytes and monocytes, evidenced by the numerous emigration pictures seen, with a small quota of homoplastic differentiation products of preexistent or previously extravasated lymphoid cells. They found that as a rule the perivascular infiltrations in the various types of syphilis are decidedly less marked than in polioencephalitis or acute epidemic encephalitis. The migration of the lymphoid cells in the vicinity of blood vessels so characteristic of encephalitis is lacking in syphilis. The large mononuclear, hyperplastic and polyblastic differentiations of lymphocytes are much less frequent in syphilis than in encephalitis. Macrophages are found in the same proportion. The syphilitic lesions show a high ratio of plasma cells and a striking frequency of mast cells, both of the plasma-mast cell type and of the histogenous variety. The greatest number of plasma cells is found in paresis. The plasma cells represent the terminal differentiation stage of lymphocytes and monocytes; they may also differentiate into plasma-mast cells as originally outlined by Krompecher. Associated with the degeneration of the plasma cells is the formation of Russell bodies (hyaline bodies) which on disintegration of the cells become scattered in the tissue. They are always acidophilic. They vary in size from eosinophil granule-like structures to giant spheres of monocytic proportions. The authors believe that in no way does the vascular or the newly formed capillary endothelium give rise to free wandering phagocytic cells. Extravasation of red corpuscles into the adventitial spaces occurs rarely in syphilis, but in areas of softening it may be massive. Polymorphonuclear and eosinophilic leukocytes play practically no rôle in this inflammatory process, but the latter may be extremely numerous in areas of softening. They believe that the formation of compound granular cells occurs occasionally about vessels and that it is extremely marked in areas of softening in which emigrated lymphocytes may become transformed into gitter cells.

WINKELMAN, Philadelphia.

A CASE OF SUPERIOR HEMORRHAGIC POLIO-ENCEPHALITIS WITH TONIC LABYRINTHINE AND CERVICAL REFLEXES ON THE EYES. O. SAGER, A. KREINDLER, G. DINISCHIOTU and D. O. VASILIU, Rev. d'oto-neuro-opht. **7**:504 (July) 1929.

A patient with hemiparesis of the left side was admitted to the hospital on Oct. 13, 1928, with the following history: On October 26, while drunk and fighting, he suffered a blow on the head which rendered him unconscious; he regained consciousness on the next day but was paralyzed on the left side. When examined, the patient was somnolent but easily aroused; he had severe headache; the pulse rate was 60, and the respiration 24. The tendon reflexes on the left side were exaggerated when the patient was awake, and diminished when he was asleep. The abdominal and cremasteric reflexes were absent on the left.

There was a bilateral Babinski sign, with ankle clonus on the left. No movement of the left arm was possible; movement of the right was possible but segmental force was diminished. There was slight contracture on the left side. The cranial nerves, eye grounds and pupillary reflexes were normal; the pupils were equal. The spinal fluid was normal.

Ten days later, the patient went into a profound stupor. The reflexes were now feeble, now lively. Tonic neck and labyrinthine reflexes on the eyes (Magnus) were present. There were bilateral ptosis, paresis of the right external rectus, and nystagmus on looking to both the right and left. Respiration was full and at times deep, at other times superficial. The tendon reflexes were lively during full breathing, but were diminished during superficial respiration. There was incontinence of urine.

The patient showed progressive improvement and was discharged as cured on Dec. 20, 1928.

The diagnosis is supported by the etiology (alcoholic excess) and the coexistence of ocular paralyses with a state of somnolence, although the ocular paralyses did not appear until fourteen days after the onset. To be noted are the cervical labyrinthine reflexes on the eyes and the rôle played by the gray matter around the ventricles and aqueduct of Sylvius in sleep. Bárány has noted cervical reflexes on the eyes in the new-born, and Kleyn and Stevens in an infant with cerebral tumor.

DENNIS, Colorado Springs, Colo.

CHANGES IN THE CENTRAL NERVOUS SYSTEM IN RECKLINGHAUSEN'S DISEASE. E. GAMPER, J. f. Psycho. u. Neurol. **39**:39, 1929.

The patient was a woman, aged 31, whose father had died of leukemia; the maternal grandmother had married her uncle; the mother had had several attacks of manic-depressive psychosis; two maternal uncles had committed suicide. According to the patient, she developed, early in life, general pigmentation of the body, which was attributed to disease of the liver. During childhood, she had measles, scarlatina, diphtheria and jaundice. At the age of 5, she had pericarditis and at 28 and at 29 slight attacks of grip. Menstruation did not appear until she was 23, and was always irregular and scanty. Intellectually, she was below the average. She had frequent attacks of dyspnea, palpitation and pains in the precordial area. She was admitted to the hospital two weeks before death, with symptoms and signs of a nonlocalizable expanding intracranial lesion. Necropsy confirmed the diagnosis of Recklinghausen's disease. The anatomic changes in the central nervous system were: neurinomas of both vagus trunks; multiple gliogenous tumors of the ventricles associated with neuro-epithelial proliferations; two subependymal tumors of neurinomatous structure which, owing to their ganglion cell content, resembled the ganglioneuromas; a circumscribed blastomatous gliomatous proliferation in the left dorsal accessory olive; glial infiltration in the region of the spinal root and ganglion of the left trigeminus; considerable partly dysgenic and partly blastomatous changes in the tegmentum of the midbrain; an accumulation of pigment associated with proliferative changes in the glia of the reticular zone in the substantia nigra and in the left globus pallidus; a peculiar sclerosing process with blastomatous cell proliferation and diffuse loss of myelin fibers in circumscribed areas of both frontal lobes and cerebellum (especially the vermis), associated with dysgenic anomalies; and circumscribed nodular formations in individual cerebellar lobules, resembling the nodules of tuberous sclerosis. The mesenchymatous tissues showed: local circumscribed areas of undifferentiated tissue in close relation to similar changes in the nerve parenchyma; hyperplastic thickening of the leptomeninges; angiomatous formations of the vessels, and extensive regressive changes in the walls of the latter.

KESCHNER, New York.

STUDIES OF COLORED AUDITION. G. MARINESCO and SAVA VASILE, Rev. d'oto-neuro-opht. **7**:500 (July) 1929.

The association of an auditory with a visual sensation is rare in normal adults but more frequent in pathologic cases. It consists in the appearance of visual

images, usually geometric forms, following the pronunciation of certain sounds: vowels, consonants, names of persons, days of the week or isolated notes of the violin. Several cases are cited. Of fifteen pupils (acquired blindness) in a school for the blind, 13.3 per cent were affected; of thirty-eight blind in an asylum, 7.9 per cent; seven artists were found with colored audition. A physician, aged 30, had a marked case of colored audition. Single low tones of the piano had a blue color; in a chord, they were gray; high tones were red. A locomotive whistle produced the image of a bright yellow cone; Chopin, that of washed-out colors; Wagner, green; English and German call up black; Russian, gray; French, deep red, and Roumanian, black mixed with red. In taste sensations sweet and salt were neutral, while bitter made the patient think of black.

Several theories in explanation of this phenomenon are discussed. The authors believe that this is a psychologic condition. It is a predisposition which is associated with a greater impressionability of the auditory centers for words and of mental vision. Colors associated with vowels, names of countries, etc., are specific for the same person. It is extremely rare for color sensations to be associated with all words heard.

Colored audition depends on the psychic state. Preferential associations play an important rôle. One remembers certain things encountered only once but which are deeply engraved on one's mind. Thus, one patient associated Sunday with red because on the calendar Sundays are printed in red ink. In the majority of patients the color representation is only mental, but a number of the patients who are blind project the vision outwardly. Thus one patient sees the image in front of his face to the right and above his head. In one case, the sensibility was so marked that the patient colored words when she wrote them or read them to herself. When she read mentally, she heard the words as plainly as if they were spoken.

DENNIS, Colorado Springs, Colo.

HALLUCINATORY "COLOR HEARING." VLADIMIR VUJIĆ, Jahrb. f. Psychiat. u. Neurol. **46**:262, 1929.

A farmer, aged 42, received, in 1915, an injury to the right side of the skull which rendered him unconscious for several weeks. Three years later, he developed generalized convulsions. In 1925, he was admitted to the insane asylum in Belgrade. During his stay in the institution, he had, almost every month, a severe attack of grand mal and was continuously irritable, aggressive and forgetful; he also showed a definite defect in intelligence. Neurologic examination yielded negative results as did the Wassermann test of the blood and cerebrospinal fluid. In June, 1928, the patient complained that for a considerable period immediately before the attack of grand mal he had "perceived golden yellowish whistling," and had heard it simultaneously and equally in both ears. No photisms and no phonisms could be elicited; in other words, he had experienced during the epileptic aura "audition colorée," or elementary acoustic hallucinations. As a result of the observations in a previously reported similar case and from a study of the literature, Vujić believes not only that audition colorée may be intensified by pathologic processes, but that in some cases secondary perceptions may appear also exclusively only during some pathologic processes.

KESCHNER, New York.

THE FUNCTIONAL CAPACITY OF TRANSPLANTED ADULT FROG EYES. CLYDE E. KEELER, J. Exper. Zool. **54**:461 (Nov. 5) 1929.

Koppányi's tests for vision in transplanted rat eyes are inadequate. Iris contraction is not a proof of vision. Iris contraction may be elicited from eyes of blind mice and from the excised irides of lower vertebrates. The best published record in door choice tests made by one of Koppányi's rats with a transplanted eye is not statistically significant. The jumping test does not distinguish between seeing and blind rats or mice. This test depends theoretically on judgment of distance based on clear visual imagery, whereas there is no definite evidence that normal rats can distinguish form.

The recording of action currents to test the visual capacity of transplanted eyes is proposed. The action current method was applied to transplanted adult frog eyes. The best of these produced only a 0.12 millivolt change in potential when stimulated by a light of 441,235 micrometer candles, which is 245 times as much light as is necessary to elicit the same amount of response from a normal eye. Such a transplanted eye with the optic nerve intact could not function as an organ of vision.

WYMAN, Boston.

HETEROTRANSPLANTATION IN HOMOSEXUALITY. KUROW, Wratsch Djelo, vol. 11, no. 20.

Observations were made on a woman, aged 27, at the Psychiatric Institute of Charkow. As far back as the patient could remember, she had an aversion to girls' clothing and preferred to wear that of boys. She also preferred to play with boys and disliked girls' games. She came more and more to wear men's clothing exclusively, and since youth had felt a love feeling toward members of her own sex. At the age of 13 she was sexually abused by a man; afterward she lost all interest in men, her passion becoming definitely directed toward her own sex. No further heterosexual experiences occurred after the age of 13. She became much attached to one woman who had a definite feminine habitus. Her voice and face and manners approached the masculine; pubic and axillary hair was scanty; the external genitalia were normally female. The ovaries were not palpable. No menses were described during the period of observation. Transplantation of ovaries from the sheep and the pig were made under the breasts, but the transplants were not resorbed until the third month. No psychic or physical change was observed after this operation.

HART, Greenwich, Conn.

A STUDY OF THE IRIS MECHANISM OF THE ALLIGATOR. MAY SCHAEFER ISKE, Anat. Record **44**:57 (Oct. 15) 1929.

The course of the oculomotor nerve of the alligator and the turtle is described. Histologic examination reveals a striated iris muscle in the alligator. Its innervation is similar to that of the smooth iris constrictor of mammals. This was determined by the action of atropine, pilocarpine, nicotine and curare. Each drug was applied locally into the conjunctival space. Nicotine was also injected intravenously, and it was used to paint the ciliary ganglion. Curare, besides being applied locally, was injected intraperitoneally. A tested electric current was used as a stimulus. A dilator muscle was not found to be present. Evidence indicates that dilatation is produced by elastic tissue.

The iris musculatures of the turtle were used for comparative purposes. The results of the experiments on the turtle were similar to those for the alligator, while those for the pigeon were such as would be expected for striated muscle.

ISKE, Indianapolis.

TREATMENT OF CHOREA MINOR WITH INTRAVENOUS INJECTIONS OF SODIUM SALICYLATE. LOPEZ AYDILLO, Arch. de neurobiol. **9**:69 (Jan.-March) 1929.

The author has used intravenous injections of sodium salicylate with great success in the treatment for chorea minor. Ten cubic centimeters of the solution (sodium salicylate, 10 Gm.; pure dextrose, 5 Gm.; sterilized distilled water, 100 cc.) was injected every two days until complete cure obtained. The latter was effected in six cases with less than twenty injections. In two other cases, one patient showed complete recovery before the twentieth injection although the curative process was not so rapid, while the other was practically cured after thirty injections. According to the author, the choreic movements of the tongue resist the treatment more than the other symptoms. No accident was observed in any of the eight patients during the period of treatment.

NONIDEZ, New York.

DIFFERENCE BETWEEN THE REACTION OF NORMAL AND TABETIC PERSONS TO PLETHYSMOGRAPHIC (PSYCHOPHYSIOLOGIC) EXAMINATION. H. DE JONG and J. PRAKKEN, Acta psychiat. et neurol. **4**:65, 1929.

The authors regard the plethysmogram as an index of the tonus of the autonomic nervous system. They compared the reaction of normal persons with that of persons with tabes in order to determine if certain tabetic symptoms, hypotonia, arthropathies, etc., might not be due to involvement of the autonomic system. They examined seven normal persons and twelve persons with tabes. In 83 stimulations (either psychic or sensory) of the normal persons, 77.1 per cent showed a normal plethysmographic curve, while of the same number of stimulations of patients with tabes, the curve was normal in only 3.6 per cent. In the remainder, the curve was of the spastic or semispastic type. This indicates the presence of a heightened autonomic tonus in tabes. PEARSON, Philadelphia.

INTERNAL HEMORRHAGIC PACHYMENINGITIS IN YOUNG CHILDREN. FRED C. HUNT, Am. J. Dis. Child. **39**:84 (Jan.) 1930.

Virchow, who first described internal hemorrhagic pachymeningitis, thought that the hemorrhage was secondary to subendothelial proliferation. For a time, however, it was generally held that the hemorrhage was primary. Recently, pathologists have returned to Virchow's point of view. The condition is more common in children than might be thought, and is characterized by an acute attack, in which the symptoms are usually of a convulsive nature, followed by a quiescent period of varying duration and then by the appearance of sequelae. The sequelae include hydrocephalus, visual defects, orthopedic deformities and, especially, mental retardation. Hunt describes six cases of hemorrhagic pachymeningitis, in one of which an autopsy disclosed a subdural clot in the parietal area. The other five patients lived, four with mental retardation. DAVIDSON, Philadelphia.

THE RÔLE OF ANXIETY IN THE PSYCHOSES AND PSYCHO-NEUROSES. HENRY YELLOWLEES, Brit. J. M. Psychol. **9**:26 (May) 1929.

The author, as his contribution to the joint meeting of the Psychiatric Section of the Royal Society of Medicine and the Medical Section of the British Psychological Society, discusses the part played by anxiety in psychoneuroses and psychoses. He expresses the belief that morbid anxiety plays a rôle of first importance in psychoneurosis and agrees whole-heartedly with the psychoanalytic theories as to the causation of anxiety states in these conditions. However, on the basis of a comparison between the behavior of psychotic persons and Freud's own contributions to the theory, which the author cites at some length, he does not believe that anxiety plays more than a minor rôle in psychotic conditions, even in involutional melancholia. PEARSON, Philadelphia.

STEREOSCOPIC PHOTOGRAPHS OF THE FUNDUS. A. ZAMENHOF, Ann. d'ocul. **166**:689 (Sept.) 1929.

Zamenhof describes a technic for taking stereoscopic photographs of the ocular fundus. He obtains the stereoscopic effect, as Bedell does, by displacing the camera laterally. He first takes a picture as far to the right as it is possible to obtain a clear image of the fundus, then displaces the camera as far to the left as possible. He believes that stereoscopic photography of the fundus is a valuable method of recording changes and has the advantage of being much less time-consuming than the more tedious method of drawing. The principal objection is that the photographs are not in color. The four illustrations show papilledema, albuminuric neuroretinitis, metastatic carcinoma of the choroid and atrophy of the optic nerve. BERENS, New York.

SPINAL FLUID IN CERTAIN MENTAL CONDITIONS. A. COURTOIS, Ann. méd. psychol. **3**:218 (Oct.) 1929.

The author believes that changes in the cerebrospinal fluid are often overlooked because of their fleeting nature. He reports a study of the spinal fluid in "mental confusion," dementia praecox and the depressed form of manic-depressive psychosis. Courtois finds that there is an average count of 9 or 10 leukocytes

in "confusions" and in schizophrenia; a trace of albumin is present in almost all of these and a definitely abnormal amount (40 or 50 mg.) in the dementia praecox and cyclothymic disorders. Increased globulin is found definitely in these two psychoses. Courtois considers that his observations are evidence of the organic nature of these mental diseases and likens them to encephalitis.

DAVIDSON, Philadelphia.

"SCHIZOPHRENIC" PSYCHOSES IN METENCEPHALITIS. ERICH GUTTMANN, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:575 (Feb. 11) 1929.

The schizophrenic psychoses in encephalitis may be divided into four groups: (1) the symptomatic psychoses in an acute or subacute brain process, similar to all other symptomatic psychoses; (2) a group with clouding of consciousness indicating a cerebral process which can produce exogenic syndromes, but in which delusions are still retained; (3) a group of stationary cases characterized by changes in personality of a paranoid type, and with more or less systematic delusional formation; (4) a group which is not a true schizophrenic group but which is allied to these psychoses.

ALPERS, Philadelphia.

SPINAL RECKLINGHAUSEN'S DISEASE. L. CORNIL and P. MICHON, Encéphale **24**:765 (Nov.) 1929.

A boy, aged 15, showing the usual characteristics of multiple neurofibromatosis, also had the symptoms of a complete transverse lesion of the cord in the low thoracic area. Iodized oil and roentgen studies confirmed the neurologic estimate of the level and demonstrated a complete block. While surgical intervention was being considered, the symptoms improved and the boy was discharged, able to walk. The interesting features in this case were the satisfactory use of iodized oil for localization, the appearance of the neurofibroma within the spinal canal and the improvement in the symptoms.

DAVIDSON, Philadelphia.

TWO CASES OF SPASM OF THE CENTRAL ARTERY OF THE RETINA. A. RIFAT, Ann. d'ocul. **166**:711 (Sept.) 1929.

Two cases of spasm of the central artery of the retina are reported by Rifat. In both instances the patients were young, apparently in perfect health and with no history of similar trouble in their families. In the first case the return of vision was not complete. In the second case the spasm of the artery was so great that retinal edema was noted with the characteristic red spot in the macula. The nerve did not regain its normal color for two months. Retrobulbar injections of atropine were used as suggested by Abadie, who thought that they gave brilliant results in similar cases.

BERENS, New York.

SYPHILIS OF THE BASAL GANGLIA. C. I. URECHIA and S. MIHALESCU, Encéphale **24**:749 (Nov.) 1929.

This article contains a presentation of two patients with parkinsonism and a history of syphilis; they had irregular pupils, positive serologic tests and attacks of delirium, with a suggestion that syphilis is partly or in whole responsible for the basal ganglia lesions.

DAVIDSON, Philadelphia.

A CASE OF ANNULAR SCOTOMA DUE TO QUININE. GIOVANNI LODDONI, Ann. d'ocul. **166**:733 (Sept.) 1929.

Loddoni states that this is the first record of a case of annular scotoma attributable to quinine, although Mosso has suggested the possibility of this type of scotoma. He believes that the annular form of scotoma is the result of degeneration of the retina, but he is not certain just how the quinine acts.

BERENS, New York.

THE PSYCHOLOGY OF THE PSYCHOTHERAPIST. EDWARD GLOVER, Brit. J. M. Psychol. **9**:1 (May) 1929.

This masterly paper on the mechanism of the weapon — himself — which the psychotherapist uses in the treatment of his patients, should be read in the original rather than in an abstract.

PEARSON, Philadelphia.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Regular Meeting, Oct. 17, 1929

DONALD J. MACPHERSON, M.D., *President, in the Chair*

THE DISTRIBUTION OF NONELECTROLYTES BETWEEN THE BLOOD AND THE CEREBROSPINAL FLUID. DR. J. R. COCKRILL.

There are two theories as to the nature of the cerebrospinal fluid: one that it is an active secretion, the other that the fluid is a simple dialysate of the blood plasma formed by capillary pressure filtration. The evidence bearing on these two views has been reviewed by F. Fremont-Smith who comes to the conclusion that the evidence as a whole is overwhelmingly in favor of dialysis. Most of the evidence on which this conclusion is based comes from a study of the distribution of chlorides and other electrolytes between the plasma and the cerebrospinal fluid. The evidence which is offered concerns for the most part the distribution of a single ion, but it seems impossible to obtain certain data on the point in question except through an analysis of the total electrolyte system. On the other hand, with the organic substances or nonelectrolytes, such as urea, there is no reason to suppose that any inequality in distribution between the plasma and the cerebrospinal fluid should exist on the assumption that the latter is a filtration dialysate except that incident to the difference in the water content of the two fluids. It was the object of this investigation to study the distribution of various nonelectrolytes between the plasma and the cerebrospinal fluid in man and experimentally, and the bearing of their distribution on the current theories of formation of the cerebrospinal fluid.

All results are expressed on the basis of the concentration of the substance in question in the water of the cerebrospinal fluid and plasma or serum. The water content of these specimens was determined by drying a weighed sample to constant weight at 110 C. All samples for analysis, whether used directly or in the form of a tungstic acid filtrate, were measured by weight. In comparing the results obtained with similar figures of other investigators it should be remembered that here the distribution has been compared on the basis of the concentration of water in each fluid.

Dextrose, creatinine and uric acid are unequally distributed between the water of the cerebrospinal fluid and the water of the plasma. Dextrose was measured as the fermentable reducing substance. The distribution ratio of dextrose, however, has little significance in this discussion because of the possibility that the dextrose in the cerebrospinal fluid is utilized more rapidly than it is restored from the blood. Since the substance or substances which are measured by the "creatinine" color reaction are unknown, the only significance of the concentration in the cerebrospinal fluid is that the same reaction is given by this fluid and in higher degree by the plasma. There is a definitely higher concentration of uric acid in the plasma than in the cerebrospinal fluid. The fact remains, however, that the determination of uric acid is not of such specificity or accuracy that any certain conclusion could be drawn from the difference in the distribution of this substance between the two fluids.

The distribution of urea between the blood and the cerebrospinal fluid is both the most interesting and the most significant of the nonelectrolytes present in the blood and the fluid. The accuracy and specificity of the determination of urea are probably greater than for the determination of any other nonelectrolyte. There

is no reason to believe that it is either consumed or produced by any part of the nervous system or adjoining tissues; since it is readily diffusible and very soluble the cerebrospinal fluid with a higher water content than plasma would be expected to have a higher urea concentration if the distribution were equal. Not only is this not the case, but the cerebrospinal fluid water consistently contains less than that of the plasma. Most investigators agree that the plasma contains a slightly higher concentration. That they failed to find a greater discrepancy is undoubtedly due to not taking into consideration the difference in water content of the two fluids.

Because the use of strictly normal human material is impracticable, observations were extended to normal cats and cats in which an experimental uremia was produced by terminating the function of both kidneys. They were limited to urea because of the greater significance of results obtained with this substance. The distribution ratios of urea between the plasma and cerebrospinal fluid of normal cats bear out the results obtained on man from clinical material. In every case urea is unevenly distributed, and in one instance the cerebrospinal fluid water contained a concentration only one half that of the plasma water. With an accumulation of urea in the blood the urea concentration of the cerebrospinal fluid increased at approximately the same rate, the discrepancy in distribution remaining the same. This result lends weight to neither of the hypotheses considered here, for similar increases in the urea concentration of secretions, such as bile and milk, and pressure filtration dialysates, such as ascitic fluid and edema fluid, take place when urea accumulates in the blood.

It has been stated that there is no reason to believe that any inequality in the distribution of a nonelectrolyte, such as urea, should exist between the plasma and the cerebrospinal fluid if the latter is a filtration dialysate, except that incident to the difference in the water content of the two fluids. This is on the assumption that a similar distribution of urea exists between the plasma and a transudate and would exist between them if separated by an artificial semipermeable membrane. That this is the case seemed certain, but there is little evidence bearing directly on this point. The possibility of some unknown force which might lead to an uneven distribution, as protein on one side of the membrane does with electrolytes, made it seem desirable to test this assumption by experiment. Three specimens of plasma were dialyzed against simultaneously obtained samples of cerebrospinal fluid and the distribution of urea was determined before and following dialysis. In the presence of some unusual condition which normally maintained an unequal distribution of urea between the plasma and a dialysate spinal fluid, the distribution ratios should remain the same after dialysis. In the absence of the equal or greater capillary pressure of the organism some water naturally was drawn into the plasma by the colloidal osmotic pressure of the protein until the limit of distention of the collodion sac containing the plasma was reached. In the first two experiments, more urea passed out of the plasma than water was drawn in, for equilibrium of the two fluids was apparently not reached as the urea concentrations were still different when the experiment ended. This is even more significant, for it is the cerebrospinal fluid which had acquired the higher concentration of urea. While the two fluids separated by a collodion membrane were all allowed to stand at 2 C., the third system very nearly attained an equilibrium while the others did not, because of frequent agitation of both phases, that in the sac by glass beads and the other fluid by stirring. Northrup has recently noted the necessity for movement in dialyzed fluids if equilibrium is to be attained within a reasonable length of time. Far from supporting the dialysate theory of spinal fluid origin, these in vitro dialysis experiments indicate that the cerebrospinal fluid is not formed entirely in this manner.

Conclusions.—It must be admitted that there are certain inequalities in the distribution of electrolytes between the plasma and cerebrospinal fluid of such a nature as would compensate for the presence of protein in considerable amounts in one of the fluids, and which suggest strongly that the spinal fluid is in the

nature of a dialysate. It has been shown here, however, that certain nonelectrolytes, particularly urea, are likewise unequally distributed between the two fluids and in such a manner that it is difficult to conceive of the spinal fluid being formed entirely by plasma ultrafiltration.

The electrolyte equilibrium which exists is not incompatible with the assumption that the spinal fluid is a secretion. It may be looked on solely as the mechanism for bringing the osmotic pressure of the cerebrospinal fluid to approximately that of the plasma, just as the bile, concerning which there is no argument that it is a secretion, has essentially the same osmotic pressure as the plasma. It is not intended to present these observations on the unequal distribution of urea as evidence in favor of the secretion theory so much as in opposition to the idea that the spinal fluid is solely an ultrafiltrate.

DISCUSSION

DR. FRANK FREMONT-SMITH: If it can be established that any substance is distributed between the cerebrospinal fluid and plasma in a manner not consistent with the laws of diffusion, then dialysis fails to explain the composition of the cerebrospinal fluid so far as that substance is concerned. Therefore, Dr. Cockrill's studies in regard to urea are challenging. I can find no criticism of her methods of analysis nor in her presentation. There are, however, certain possible pitfalls of interpretation which deserve scrutiny because of the significance of her conclusions. Dr. Cockrill has found that the human cerebrospinal fluid contains only from 50 to 80 per cent of the urea found in the plasma (calculated as urea in the water of plasma or cerebrospinal fluid). Cullen and Ellis (*J. Biol. Chem.* **20**:511, 1915), however, found the urea in the cerebrospinal fluid within 2 mg. of that of the blood in more than 60 per cent of thirty-two cases. Therefore, I hope that Dr. Cockrill will be able to extend her data to include a larger series of cases than she has reported.

Dr. Cockrill states that "there is no reason to believe that any inequality in the distribution of a nonelectrolyte such as urea should exist between the plasma and the cerebrospinal fluid if the latter is a filtration dialysate, except that incident to the difference in the water content of the two fluids." This statement is based on the assumption that the sample of plasma obtained at the time of lumbar puncture fairly represents the urea content of the plasma during the period in which the spinal fluid was formed in the ventricles and was finding its way to the lumbar sac. A variation of a few milligrams in the urea content of the plasma during this period would lead to an apparent inequality in the distribution of urea between plasma and cerebrospinal fluid, in samples obtained at the time of lumbar puncture. One needs assurance, therefore, that the urea content of the plasma has not varied during a period of perhaps eight or twelve hours, preceding lumbar puncture, i. e., a period sufficient to include the time of formation of the sample of cerebrospinal fluid studied. I know of no data on the constancy of the plasma urea content from hour to hour. Another factor which complicates such equilibrium studies is that lumbar fluid consists of ventricular fluid to which has been added an unknown proportion of fluid from the perivascular spaces of the brain and spinal cord. It would be interesting to compare the urea content of lumbar and ventricular fluid. The three dialysis experiments are open to the same doubt as to whether the samples of blood plasma studied fairly represented the composition of the blood from which the sample of spinal fluid was formed. The fact that the freezing point of the cerebrospinal fluid, i. e., its total osmotic pressure, is usually identical with that of the plasma, and that the pressure of the cerebrospinal fluid may be raised or lowered at will by experimentally changing the osmotic pressure of the blood, leaves no doubt that the cerebrospinal fluid is in close osmotic equilibrium with the plasma and that dialysis plays the chief rôle in the formation of the cerebrospinal fluid.

THE PSYCHOLOGY OF HYSTERIA. DR. JAN H. VAN DER HOOP (Amsterdam).

This article will be published in full in a later issue of the ARCHIVES.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Oct. 18, 1929

LOYAL DAVIS, M.D., *President, in the Chair*

PRESSURE NEURITIS; PERONEAL PALSY AND ULNAR PALSY AS COMPLICATIONS IN LONG ILLNESSES. DR. HENRY W. WOLTMAN, Rochester, Minn.

Neuritis not uncommonly develops in patients who are on the highway to recovery from prolonged and severe illnesses. The surprising frequency with which only the ulnar or common peroneal nerves may be involved stimulates interest. That toxic or infectious agents often possess a canny specificity in the choice of nerves is well known, and the inviting explanation that the cause of the forms of neuritis under discussion is a selective toxicity or infection, has been the one generally accepted. Infection is ubiquitous and difficult to disprove; in one-half of our cases, however, infection as the term is used clinically, could not be demonstrated.

In his excellent monograph on disorders of the ulnar nerve, Singer advanced the view that the highly organized segmental function subserved by the ulnar nerve may account for its ready vulnerability. The unprotected situation of the ulnar nerve at the internal condyle and of the peroneal nerve at the neck of the fibula, and the closeness of these nerves to bony structures must be potential sources of danger.

Singer grants that pressure may be a factor in the development of ulnar neuritis in those cases in which the arm is thrown across the bed in such a manner that the nerve is compressed by the hard edge of the bed or in which the arm is thrown over the head. In the latter case the plexus rather than the ulnar nerve alone is usually implicated. In commenting on ulnar neuritis, Seligmueller assigned some importance to pressure as a cause. Lloyd was more emphatic; in reporting the case of a patient who had had typhoid fever, he expressed the opinion that pressure rather than a toxin was responsible for such cases of palsy; however, he mentioned that he could not exclude injury by the attendants as a possible factor.

Oppenheim stated that pressure may cause ulnar neuritis in emaciated patients who are confined to bed. Writers do not grant, so far as I am aware, that compression of the common peroneal nerve between the bone and the bedding, enters into the production of neuritis of this nerve. Case histories illustrating the condition, both in the ulnar and in the common peroneal nerves, were cited.

Lüderitz, Stopford and others have observed that, in neuritis due to pressure, involvement of motility occurs before sensory disturbance. This was not true in these cases of ulnar palsy but did occur in those of peroneal palsy. Most of the patients whom I have observed, particularly those in whom peroneal neuritis developed, had been extremely ill and had lost greatly in weight and in muscle tonus. The popliteal recesses had become obliterated and the heads of the fibulas were unduly prominent. Stretching of the ligamentous supports of the knees had taken place so that partial genu recurvatum occurred. This resulted in placing the nerve in a still more precarious position, and also added a factor of traction.

Protective measures include massage, attention to the bedding, and proper support and position of the limbs. If the patients make satisfactory recovery from the primary illness, then recovery from the neuritis may be anticipated with confidence.

DISCUSSION

DR. LEWIS J. POLLOCK: What type of neuritis does Dr. Woltman believe is present? Is it wallerian degeneration that he designates as neuritis? In other words, is the condition a degeneration instead of an inflammation? Every peripheral nerve has a specific type of reaction to trauma. The radial and peroneal nerves react to slight trauma similarly. Complete paralysis of the peroneal and radial nerves may occur without sensory loss, whereas in the ulnar nerve, both motor and sensory fibers are affected and it is a rare thing to note

that sensory loss has disappeared when motor disturbance still exists. I have seen a number of cases of popliteal nerve palsy in bicycle riders using low handle-bars so that the knee struck the handle-bar. A great deal of difficulty, I think, is experienced in differentiating some cases of ulnar nerve palsy due to pressure at the elbow from brachial plexus lesions.

DR. G. B. HASSIN: Did Dr. Woltman also study carefully the condition of other peripheral nerves such as the ulnar, median, etc.? A peroneal nerve involvement may be a partial manifestation of a general nerve lesion, such as is seen in polyneuritis.

DR. ARTHUR WEIL: Histologic examinations have been made of peripheral nerves which had been compressed mechanically for a long period. The histologic changes were merely of a degenerative nature, showing demyelination. It might be of interest to cite Spielmeyer's recent publication on this subject (*Handb. d. norm. u. pathol. Physiol.* **9**:286, 301 and 336, 1929).

DR. PETER BASSOE. I think that there is ample proof that the ulnar nerve is extremely likely to be paralyzed from pressure; and we all remember the great frequency with which ulnar nerve paralysis occurred in former times, when operations were done in the patients' homes. Anesthetics were given by more or less inexperienced anesthetists, who allowed the arm of the patient to hang over the dining-room table. Even now one sees many cases in which no other factor but pressure seems to be involved. I saw a man last week on whom an operation for hernia had been performed; his elbow was accidentally compressed during the operation. The extreme frequency of musculospiral paralysis is well understood. That these three nerves should be particularly involved, the ulnar, the musculospiral and the peroneal, seems to be explained by the fact that these nerves above all others are most often compressed.

DR. HENRY W. WOLTMAN: I think Dr. Weil answered Dr. Hassin's question with regard to the pathologic changes that might occur in these nerves. I might add that these patients were carefully examined and there was no evidence of polyneuritis or of disturbance of nerves other than those mentioned. In most cases of polyneuritis one sees early and relatively pronounced weakness of the dorsiflexors of the foot, but one usually finds enough collateral evidence in cases of polyneuritis so that these two types may be distinguished fairly readily.

In answering Dr. Pollock's question, I would say that I had no opportunity to study these nerves microscopically. I think that in many instances wallerian degeneration occurs, since it took some of these nerves a long time to recover. For instance, in the case of a patient with brain abscess, it was over a year before the neuritis had recovered entirely. Dr. Pollock spoke of the individual behavior of various nerves; I have followed his important publications dealing with injuries to peripheral nerves and the phenomena observed in their regeneration with great interest.

Formerly, one saw many patients who had developed ulnar neuritis from pressure on the nerve by the hard edge of an operating table, as Dr. Bassoe remarked. Such an injury is due to carelessness and can be avoided. Patients who developed the ulnar type of paralysis had not always been very ill, but all who developed the peroneal type had been extremely ill. The point that stimulated my interest, Dr. Bassoe, was that these forms of neuritis should occur while a patient is in bed; where he is supposed to be in a safe place.

CYSTIC TUMOR OF THE THIRD VENTRICLE.* DR. GEORGE B. HASSIN and DR. JOHN B. ANDERSON.

The clinical picture of tumors of the third ventricle depends partly on their location (whether they involve its upper or lower portion) and partly on the nature of the tumor. Soft, cystic tumors will necessarily cause less marked

* The article was published in full in the January issue, 1930, of the U. S. Veterans' Bureau Medical Bulletin. The report of this case is from the Neurology Service of the Edward Hines Jr. Hospital, Hines, Ill.

pressure on the neighborhood organs than a solid tumor. In our case, for instance, though the tumor was a fairly large cyst (2 by 2 cm.) and invaded the upper portion of the third ventricle, the clinical observations were rather meager and indefinite.

A man, aged 35, entered the Edward Hines Jr. Hospital on June 6, 1928, because of attacks of numbness and itching in the head and left side of the face of about four months' duration. The attacks lasted from five to fifteen minutes, would occur several times a day and were occasionally accompanied by vomiting and muscular weakness. On several occasions, the patient had attacks of unconsciousness, one of which happened on the street. He also complained of headaches, lacrimation and pain in the eyes.

Examination revealed slight paresis of the left lower facial nerve, bilateral papilledema and constricted fields of vision. The rest of the cranial nerves, the pupils, mentality, coordination and speech as well as the roentgenograms and

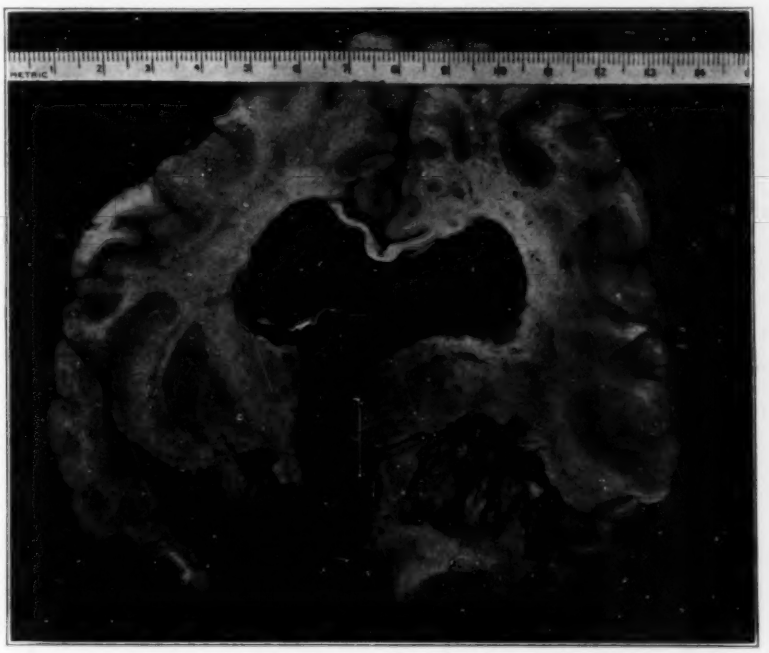

Fig. 1.—Section through the back of the optic chiasm. The upper portion of the dilated third ventricle is occupied by a tumor; the corpus callosum and the septum lucidum are thinned; the lower portion of the third ventricle is also dilated, its floor protruding.

serologic tests were all normal. A diagnosis of increased intracranial pressure was made, probably due to a tumor; the localization was indefinite. After a short period of treatment with mercury inunctions and potassium iodide, Dr. Loyal Davis, on October 12, performed a right subtemporal decompression. The tumor was not located. Nor was it located by ventriculography, which was done about four weeks later. Roentgen therapy gave a slight temporary improvement; the patient's subjective condition improved and the papilledema subsided in the left eye. During the following four months, the symptoms, especially the numbness, grew progressively worse. It became persistent, extended over the left side of the body and was associated with severe headaches. Six months after the operation, the patient died.

Of the necropsy observations we shall point out only those pertaining to the brain. It weighed 1,490 Gm. The part of the dura over the area operated on was enormously thickened; the right lateral ventricle was dilated, while the left was narrowed by a protrusion of the septum lucidum, the median wall of the lateral ventricle. The septum was elongated, folded and closely adherent to a tumor which was enclosed within its cavity (fifth ventricle). The tumor filled the upper portion of the third ventricle which was dilated while its lateral walls, the optic thalami, exhibited signs of compression but no adhesion. The tumor rested on the middle commissure, leaving the lower half free. It consisted of a gelatinous mass enclosed within a thick, smooth, connective tissue capsule. This in its turn was covered by the choroid plexus which was pushed to the side, while the corpus callosum and especially the fornices appeared thin. The pineal body, the sylvian aqueduct and the middle commissure, as well as the floor of the third ventricle, were normal.

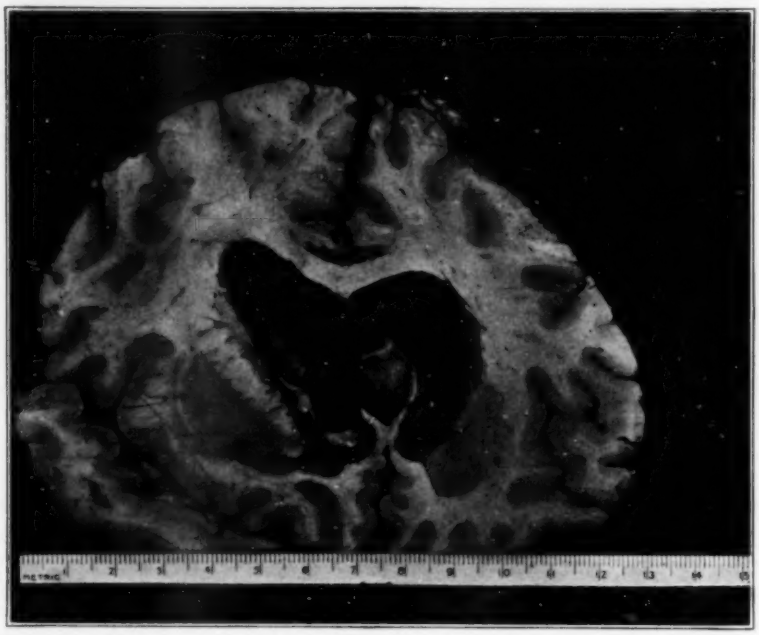

Fig. 2.—Section to the front of the optic chiasm through the anterior horns of the lateral ventricle. The tumor is enclosed within the lamina of the septum lucidum.

Microscopic examination of the tumor revealed a colloid homogeneous mass in which were scattered round structureless homogeneous cell bodies, mixed with lymphocytes, polyblasts and gitter cells. The septum lucidum itself showed, in the areas adjacent to the tumor, minute foci of softening; otherwise it exhibited no changes. Nor did the cortex show changes, except the temporal lobe in which a few lacerations were present at the site of the operation. These were caused by removal of the adjacent dura. Microscopically, the cortex here exhibited many cytoplasmic glia and oligodendroglia cells. The dura over this area showed numerous giant fibroblasts and bundles of homogeneous fibers, which remained unstained. These probably were threads used for suturing the incision. In addition, there were dense foci of lymphocytes and plasma cells which crowded the interstitial spaces of the dura and were gathered mainly around the blood vessels.

The pathologic observations may be summed up as: a cystic tumor of the septum lucidum (of the fifth ventricle); its extension to the upper portion of the third ventricle; a hyperplastic circumscribed pachymeningitis (over the site of the operation) and a reactive glial proliferation in this particular area. The primary and most important lesion was, of course, the tumor. This was responsible for the clinical picture of increased intracranial pressure which was associated with attacks of unconsciousness and paresthesias. Some of the symptoms were evidently due to occlusion of one of the foramens of Monro. They subsided after the decompression operation, while the attacks of paresthesias did not. The latter were evidently the result of pressure by the tumor on the thalamus and remained unaffected by the operation. Another feature was the failure of ventriculography to show the absence of air in the third ventricle which is rather characteristic of third ventricle tumors. Nor was the clinical picture of help in localizing the tumor. It is noteworthy how the clinical picture varies in the presence of a cyst of the third ventricle. In the case, handled by Dr. Pollock, for instance, a woman, aged 49, had a cystic tumor which occupied the same location as in our case, yet the symptoms differed. They were in the form of memory defects, stupor, articulation disturbances, dizziness and slight tremor; epileptiform attacks were absent. In the case of Guillain, Bertrand and Périsson, also a cyst, the clinical picture was dominated by decerebrate rigidity, while in one of the cases of Fulton and Bailey, though the clinical picture much resembled that in our patient, the headaches could be relieved by tilting the head. This rather suggestive phenomenon was also present in Penfield's case, in which the prominent feature was peculiar epileptiform attacks in which sympathetic manifestations were in the foreground. It seems that epileptiform attacks are the most frequent and remarkable occurrence in third ventricle cysts. This is also the impression of Högner who studied two cases and analyzed ninety-eight cases from the literature. On the other hand, in Wilson's case of a tumor of the third ventricle the patient complained of headaches and a number of attacks of fainting preceded by an aura of giddiness. The first examination revealed no indication whatever of an organic disease of the nervous system. In this connection it should be noted that in our case the tumor was large and that it probably required for its full development much more time than the duration of the patient's illness. It is most likely that a soft tumor of the third ventricle, the upper portion, may exist for some time without any symptoms whatever. When it becomes large enough, it may give an ordinary picture of increased intracranial pressure such as, headaches, papilledema and epileptiform attacks, without any additional localizing signs.

DISCUSSION

Dr. A. W. Adson: I have seen several patients with third ventricle tumors and have explored some, but I was never successful in removing them. Dr. Lillie places some stress on the studies of the eyes and bicentral hemianopia. I do not know how true this is, but in several cases I have explored on the strength of the eye changes.

Dr. Percival Bailey: Dr. Hassin did not say much concerning the tumor, but I am sure that it is a colloid cyst of the third ventricle. This is practically the only tumor that occurs in this particular situation. It is a small round body with the consistency of a rubber ball. There is usually a very thin capsule of connective tissue and a row of epithelial cells; the rest a mass of colloid. Sjövall gave the only reasonable explanation for the unique situation of these tumors. In lower vertebrates there is a glandular structure which grows from the roof of the third ventricle in the neighborhood of the foramen of Monro and is known as the paraphysis. These tumors are probably a pathologic development of this structure, which appears transitorily in the human embryo. These tumors are often described under other names. One was recently described by Penfield as cholesteatoma. I have examined sections of the tumor and he now agrees that the tumor is of this colloid type. I should like to lay emphasis on the intermittent

character of the symptoms caused by these tumors. The intermittent course is easy to understand from the situation of the tumor.

DR. GEORGE B. HASSIN: Dr. Bailey's remark about my failure to mention the type of the tumor in our case is justified. However, I confined my demonstration to those features which I could demonstrate by lantern slides, and those illustrating the histology of the tumor were not in my possession. In the complete paper the description of the tumor is given in full. As the caption reads, the tumor was cystic; it consisted of a homogeneous, colloid mass, invested by a thin fibrous capsule and contained numerous structureless cell bodies. These were mixed with lymphocytes, polyblasts, gitter cells and a few polymorphonuclear elements.

Tumors in the upper portion of the third ventricle are not always cystic, as Dr. Bailey thinks, and he himself reported a case to the Chicago Neurological Society (ARCH. NEUROL. & PSYCHIAT. **22**:614 [Sept.] 1929) in which the tumor was a glioma (astrocytoma). There is a great difference of opinion as to the exact place of origin of such tumors, and from the histologic observations alone it is not always easy to determine it.

Dr. Penfield's case came to my attention after our paper was sent to the publishers. In his case, peculiar attacks would set in and always began by the patient asking for ice. They were associated with marked sympathetic nerve phenomena, such as flushing of the face and arms, profuse sweating and salivation, respiratory difficulties (Cheyne-Stokes respiration) and by attacks of unconsciousness. The attacks were sometimes repeated and resembled status epilepticus. The necropsy revealed a tumor of the third ventricle which pressed on the optic thalami. In our case the latter also appeared slightly excavated and probably were responsible for the clinical picture of incomplete epilepsy in our patient.

INDICATIONS AND CONTRAINDICATIONS FOR SYMPATHETIC GANGLIONECTOMY IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASES. DR. ALFRED W. ADSON, Rochester, Minn.

After briefly reviewing the literature up to the present time in anatomy, physiology and surgery, Dr. Adson reviewed his own experience in treating these various peripheral vascular diseases and stressed the importance of proper selection of cases. He used the Raynaud's group as the typical class of vasospastic disorders. This was a non-occlusive group, in which the cases varied in severity from the mild asphyxias of individual digits to severe, painful, trophic lesions with gangrene. In the cases with mild symptoms which do not incapacitate the patient, he suggested that palliative measures be employed, and that sympathetic ganglionectomy and trunk resection be resorted to only when the pain becomes unbearable and the symptoms interfere with the normal activity of the patient. Before instituting surgery, even in this group, he urged that careful vascular studies be made to determine the degree of vasospasm present, in order to predict the result of the operation. The vascular studies consist in taking surface temperatures of the extremities involved, before and during the height of fever induced by the administration of a foreign protein such as triple typhoid vaccine. In persons with normal arteries and in patients with vasospastic disease it will be observed that during the height of the fever the increase in surface temperature will be from two to ten times that of the mouth temperature. This suggests that the vasomotor mechanism is capable of relaxing the normal or exaggerated tone of the arteries and arterioles, giving an index of the vasospastic phenomena as well as indicating the surgical result to be expected from ganglionectomy and trunk resection. Thus, unless the arteries are capable of dilating under the fever reaction, nothing is to be expected from the interruption of the vasomotor nerves; but if they do dilate and produce an increase in surface temperature equivalent to two or more times the increase in mouth temperature, a satisfactory result will be obtained from the operation and pain will disappear, ulcers heal, and the skin become pink, warm, and dry.

Adson and his co-workers believe that there are other diseases that result from peripheral vascular disturbances of the vasospastic type, such as thrombo-angiitis obliterans, scleroderma of the extremities, including the face and neck, and polyarthritis of young people which has failed to respond to ordinary methods of treatment.

In thrombo-angiitis obliterans, the primary lesion is a thrombosis of both arteries and veins, which may be local, bilateral or diffuse. However, there is very often superimposed on this a vasomotor spasm of the collateral arteries, relief of which will cause ulcers to heal, pain to disappear, and amputations to be unnecessary. Again caution in selecting cases is advocated, and the vascular index is used as a basis of selection.

Scleroderma of the extremities, face, and neck apparently arises from a chronic, continuous, mild vasospasm, requiring years to develop. The skin is at first cyanotic, cold and clammy. It then begins to atrophy and becomes drawn, white, hard and free from wrinkles, with ulcerations over bony prominences. The process involves the subcutaneous tissues and muscles as well, so that atrophy and limitation of muscular function soon become manifest. This lesion, like Raynaud's disease, responds to sympathetic ganglionectomy, but more caution must be employed in selecting these patients, since in the advanced cases many of the arterioles have been destroyed and nothing will be accomplished by an operation. The vascular index again serves as the basis for selection. These patients are prone to complain of muscular pains for several weeks after the operation, and these are apparently due to the sudden engorgement of the muscles with blood. The result is not only a return of warmth to the extremity, but also a restitution of the skin, subcutaneous tissues and muscular function.

Polyarthritis, involving chiefly the extremities in young persons who have cold hands and feet with excessive perspiration, is a lesion resulting from impaired circulation similar to the lesion of scleroderma, except that in this instance the bones, joints, cartilages, ligaments and muscles are affected, giving rise to pain, swelling, tenderness, muscular atrophies and spasm. Again it was argued that if local heat and vaccines which produce fever give temporary relief, it is justifiable to give permanent increase in heat by performing sympathetic ganglionectomy, which relieves the vasomotor spasm and increases the circulation, thereby relieving the pain, reducing the swelling and bringing a restitution of function to the extremity.

Case History and Pathologic Specimen of Acute Polio-Encephalomeningomyelitis. Dr. Theodore T. Stone.

History.—L. D., a man, aged 26, was admitted to the Passavant Hospital on Aug. 27, 1929, with the following complaints: paralysis of the lower extremities; weakness of the right arm; shortness of breath; inability to urinate. On Thursday, Aug. 22, 1929, the patient had had an occipital headache. On Friday night he felt ill and, although he did not take his temperature, he thought he had high fever. He slept very little. On Saturday he visited a physician who diagnosed the condition as intestinal influenza or "summer flu." After returning home in the afternoon, he felt worse and went to bed. His complaints at this time were backache and severe occipital headache.

The patient went to the bathroom several times during the evening and when doing so first noticed weakness in the legs. On Sunday, August 25, at about 4 a. m., he tried to go to the bathroom and found he was unable to stand alone. On Sunday evening, he was unable to support any weight and had to be carried from his room to one on the first floor. On Monday morning he was unable to move the legs at all and was also unable to urinate. At this time the headache disappeared and had not returned since. On Monday afternoon the temperature was 104.2 F. On Monday morning and evening he was catheterized. He came to Chicago by train from Mason, Michigan, and arrived at the hospital at 9:15 a. m., on August 27. Shortness of breath developed soon after.

Examination.—A neurologic study by Dr. Loyal Davis revealed: moderate cervical rigidity; rapid shallow breathing; flaccid paralysis of both lower extremities, with lateral motion retained at the ankle of the left; abduction of the right arm was not possible, while abduction of the left was weak; extension of the fingers was weak. The deep reflexes were absent in both lower and the right upper extremities; the abdominal and cremasteric reflexes were absent. Sensation was entirely normal, as were also the cranial nerves except for a rapid, fine, horizontal nystagmus with a quick component on the side of fixation. Mentally, the patient was alert, intelligent and cooperated well. A diagnosis of acute ascending poliomyelitis was made on Aug. 27, 1929. Dr. Bassoe confirmed the diagnosis of Dr. Loyal Davis.

Course.—The patient's condition became steadily worse. Respirations, on Sept. 2, 1929, became very shallow, irregular and labored. There was a peculiar twitching and an excessive movement of the muscles of the throat with each inspiration. The finger nails and lips became cyanotic; the pulse was full and bounding, 128 per minute. He died on Sept. 3, 1929, of respiratory paralysis. The temperature during the stay in the hospital ranged between 100 and 101 F.

Laboratory Studies.—The blood showed: red cells 6,430,000; white cells 24,400; hemoglobin 80 per cent; differential count: polymorphonuclear neutrophils, 78 per cent; lymphocytes, 17 per cent; transitional cells, 5 per cent. The spinal fluid was clear; pressure was 140 mm. of water; jugular compression caused a rise to 230 mm.; globulin tests were positive; the cells numbered 114 mononuclears (lymphocytes) per cubic millimeter.

Necropsy.—A postmortem examination was made three hours after death. The macroscopic changes were: Brain: the leptomeninges showed no abnormalities except some adhesions to the longitudinal sinus in the superior medial aspect of both hemispheres. Grayish granular nodules were found in this area. The entire brain was studded with many punctate hemorrhagic points situated in both the gray and the white matter. In the regions of the basal ganglia, external capsule, claustrum and the Island of Reil, especially on the left side, small pinhead sized hemorrhagic cavities were seen. Here also there were many punctate hemorrhagic points. These cavities were either distended blood vessel spaces or cavities filled with blood.

Spinal Cord: The dura was closely adherent to the entire spinal cord and was of a reddish brown tinge over the cervicodorsal region. Section of the cord at the level of C5 showed a marked prominence of the gray matter, of the anterior more than of the posterior horns. The gray matter was a dark brownish red, and, especially in the anterior horns in the lower dorsal and lumbar regions, showed a change similar to that found in the cervical region. The gray matter throughout the entire spinal cord was softer than normal.

Microscopic Study: The entire brain showed a moderate disturbance of the architectonic structure of the cortex. The ganglion cells showed neuronophagia. The blood vessels were thickened and there was a marked distention of the blood vessel spaces. All the blood vessels contained a perivascular round-cell infiltration consisting of mononuclear leukocytes, lymphocytes, gitter cells and plasma cells. In the region of the basal ganglia there were many cavities which appeared to be punched out spaces with no reaction of any kind about them. There was no columnar lining in these spaces. There were a considerable number of distended vascular spaces also. The capillaries were distended and filled with blood elements. There was proliferation of the endothelial and adventitial cells. Hemorrhage was seen along these distended capillaries.

The spinal cord, especially the anterior horns, showed complete softening. The posterior horns were softened also, but to a less degree. In the upper dorsal region a few ganglion cells were seen in the posterior horn; these, however, showed acute changes. The softened areas consisted chiefly of gitter cells. The blood vessels showed perivascular round-cell infiltration. Herxheimer scarlet red stain showed that the anterior horns were made up almost entirely of fat. The central canal was distended.

The leptomeninges contained an infiltration of cells made up of large mononuclear cells, macrophages, lymphocytes and plasma cells. The subarachnoid space was distended. The blood vessels were thickened and distended. The cerebellar hemisphere showed no abnormalities.

Diagnosis.—The histopathologic diagnosis was acute polio-encephalomeningomyelitis.

DISCUSSION

DR. G. B. HASSIN: The slides showed beautifully the perivascular infiltrations. I wish to know only whether there were any inflammatory cells present aside from gitter cells, and what were the observations on spinal puncture.

DR. PERCIVAL BAILEY: Dr. Stone made a very extensive and comprehensive anatomic diagnosis, but did not mention the etiologic diagnosis. I wonder what is the cause of those peculiar inflammatory lesions which are seen so commonly at present. Some patients get well and some do not. These cases are reported all over Europe, and are becoming numerous here. Dr. Stone did not attempt to tie this case up with epidemic encephalitis or poliomyelitis, but this relationship must certainly be considered.

DR. PETER BASSOE: Is there any reason why this could not be an infection with the virus of ordinary epidemic poliomyelitis? It seems to me that cases reported have shown similar changes, with extensive degeneration. Has Dr. Stone found out whether there were any cases of poliomyelitis in that neighborhood?

DR. CHARLES F. READ: I saw a similar case some years ago in a man, aged about 21, who died from five to seven days after the onset of the illness. The spinal fluid was normal and other signs the same as those described by Dr. Stone. Dr. Hassin's examination of the cord showed profound lesions in the anterior horn, with much extravasation extending up to the medulla. He believed it to be a case of poliomyelitis, and this opinion was shared by Dr. Hektoen. This case occurred also where there was no epidemic. Artificial respiration kept the boy alive for about three days after he would otherwise have died.

DR. THEODORE T. STONE: The laboratory studies in the blood showed 24,000 leukocytes. The urine was within normal limits. Microscopically, there was evidence of inflammatory cellular elements, large lymphocytes, small lymphocytes and a few polymorphonuclears.

I neglected to mention that the boy was fortunate in having Dr. Bassoe and Dr. Loyal Davis see him. An inquiry of the physician at Mason, Michigan, elicited the answer that he had not seen any cases of poliomyelitis. I do not know whether there have been any cases since then or not.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Oct. 25, 1929

C. A. PATTEN, M.D., *President, in the Chair*

ANNIVERSARY OF DR. S. WEIR MITCHELL'S BIRTH.

Since the centennial anniversary of the birth of Dr. S. Weir Mitchell is about at hand, Dr. Mills made the following proposal: "I think it highly important that this society should take some steps in regard to the matter. Dr. Mitchell was president of the society during the early days of its existence, the first five or six years, and contributed many things of importance. I move that the Society celebrate the anniversary of his one hundredth year next December with a series of papers which will have reference to him and to the work which he has done.

I think it would be wise if the Chairman would appoint a committee of the older members to attend to this. I therefore move that this step be taken."

The motion was seconded by Dr. Francis X. Dercum.

The president, Dr. Patten, appointed the following committee: Dr. C. K. Mills, chairman; Dr. W. G. Spiller, Dr. F. X. Dercum, and Dr. F. H. Leavitt, secretary of the Society.

THE RESULTS OF THE WILLIAMS OPERATION FOR RELIEF FROM FACIAL TIC. DR. CHARLES H. FRAZIER and DR. A. M. ORNSTEEN.

DR. ORNSTEEN: A man, aged 46, began to have attacks of blepharospasm in the early part of 1927; they became progressively more severe and more constant until the patient was incapacitated for work. The first manifestation was in the form of periodic closure of the eyelids which lasted several minutes and occurred several times a day; there were occasional free days. There was a dropping of the upper lid which was readily overcome by voluntary elevation of the lid. From the beginning the manifestation was bilateral. With the progression of the condition it became evident that the mechanism was not merely a periodic ptosis, but was rather an orbicular spasm. The attacks gradually became almost constant and the patient repeatedly picked at the upper lids in order to lift them, without effect. Of late, he has been unable to read or visit the theater or the movies, and he has had to give up driving a car.

About fifteen years before presentation, he had evidence of nephritis with backache and vertigo for which all teeth and the tonsils were removed. Several years previous to presentation, he was troubled with pruritus of the extremities and ears, following which there appeared a group of blisters on the left forearm and later several large furuncles in each axilla, which apparently was precipitated by the partaking of a large quantity of ice cream. It was at this time that diabetes was recognized. On a self-instituted strict diet, he lost 50 pounds (22.7 Kg.) in ten weeks. It was after he had lost the first 25 pounds (11.3 Kg.) that the ocular manifestation first appeared.

He then visited a number of oculists, ophthalmologists, internists and neurologists in Philadelphia and New York. Several opinions were that the case was one of diabetic myasthenia, indicating that the condition was a pseudoparalytic ptosis rather than a spasm; or postencephalitic blepharospasm, although there was not a single indication of encephalitis aside from the blepharospasm.

I was convinced from the beginning of my observation that there was a definite spasm of the orbicularis oculi rather than a ptosis. I believed that the spasm was a functional manifestation released by the factors of exhaustion, metabolic disorder and conditioning of the reflexes, as follows: For many years the patient had been engaged in the wholesale produce business, necessitating his being at the wharf in the early morning hours. After only two or three hours of sleep he would go to work on a trolley car; during the ride a strong desire for sleep overcame him and in order not to pass his destination he frequently forced up the upper lids to watch the passing streets, while the sleep mechanism continually forced the eyes to close. This continued over a period of years, thus developing and rather fixing an abnormal reflex mechanism. The effect of focal infection (tonsillar and dental, with nephritic involvement) and later the metabolic disorder (diabetes) very likely produced cellular changes in the midbrain or interbrain, fixing the conditioned reflex outside of the will as an automatic spasm.

It is interesting to note that orbicular spasm, as well as upward oculogyric crises, occurs in epidemic encephalitis. Elevation of the eyeballs and upper lids occurs independently or in association with orbicular spasm, which indicates an intimate anatomic relationship between the neural mechanisms. The normal movement of closing the eyelids is also accompanied by upward rotation of the eyeballs, further indicating the close association of these two movements. In this patient, the spasm of the orbicularis oculi muscles was associated with upward rotation of the eyeballs, as was readily seen when he attempted to overcome the spasm

by forceful elevation of the upper lids. This associated movement does not occur with unilateral facial spasm, in which the condition is often accompanied by a mild closure of the eyelids of the unaffected side, merely because of the bilateral cerebral control of this part of the face, but which does not indicate involvement of the opposite side. Therefore, I believe that this patient's condition is a central one and is caused by involvement in the same centers as in the encephalitic cases. It may be referred to as a functional disturbance of the diencephalon where the physiologic centers for this type of ocular movement lie, namely, in the region of the anterior quadrigeminal bodies from which the facial nuclei and the ocular motor nuclei receive their impulses in turn in the production of this associated spasm.

In order to cause the cessation of the automatic spasm it was thought advisable to paralyze the orbicularis oculi by cutting their nerve supply. This was done by Dr. Frazier, who will give the details of the surgical aspect of the case.

DR. FRAZIER: May I remind you of the various proposals made from time to time for relief from blepharospasm? In 1901, Kennedy proposed anastomosis of the facial nerve to the spinal accessory nerve. In 1906, Speville was the first to advise the injection of alcohol into the facial nerve, on this occasion at the stylomastoid foramen; later, he proposed stretching of the nerve at the same site. Sicard, in 1918, proposed injection into the facial nerve peripheral to this foramen. Coppez, in 1921, and Sachs, in 1925, proposed two rather complicated plastic operations, one on the orbicularis oculi muscle, the other on the upper lid. Finally, in December, 1928, Dr. Henry Ward Williams of Rochester, N. Y., one time intern at the University Hospital, published his experiences, and it was because of his activities and suggestions that our interest in this subject was revived.

My early experiences with the treatment for blepharospasm were anything but happy. On several occasions I have injected alcohol into the facial nerve, but not always effectively. This method, however, has no real merit; at best it can yield only transitory results and for a while leaves the patient with the distressing disfigurement of a facial paralysis. I can see nothing in the alcoholic injection, whether given at the foramen or peripherad, that appeals to me as a reasonable solution of the problem. Dr. Williams, in two of his three patients, used alcoholic injections at first but concluded that if permanent results are to be obtained the nerves must be divided.

In the case which Dr. Ornsteen presented, the blepharospasm was bilateral. I operated on both sides at one sitting, but had to repeat the operation on the left side. Through an oblique incision between the superior margin of the parotid gland and the orbit, I exposed the three branches of the upper division of the facial nerve as they make their exit from the parotid gland. The twig that is given off from the buccal nerve was left intact. The results, as you have seen, are eminently satisfactory. The spasm of the left eye has been entirely relieved and in the right eye there is only a quiver, not sufficient to close the eye. At all events, the patient is content in that he is able to conduct his business affairs without handicap.

DISCUSSION

DR. WALTER FREEMAN: Would it be possible to do a modified Stoffel operation on the various fasiculi of the nerve, thereby partially paralyzing the face without leaving permanent paralysis?

DR. WILLIAM G. SPILLER: The patient presented by Dr. Frazier and Dr. Ornsteen was referred to me by Dr. Gurin. The blepharospasm was so pronounced that at times the patient was forced to close his eyes while walking through traffic and he was in danger of being injured. I requested Dr. Fay to attempt the injection of alcohol into the branches of the facial nerve supplying the orbicularis palpebrarum on each side. It seemed wise to do this before resorting to a more radical procedure such as cutting the nerve supply, in order to determine whether such treatment would accomplish the desired result, but I believed that the paralysis which would result from the alcohol would be only

temporary. Some information then came to me regarding the operative procedure adopted by Dr. Williams. He sent me a description of his technic; this was before his paper appeared. The patient then passed under the care of Dr. Frazier.

Dr. Hugh T. Patrick was one of the first in this country to inject alcohol into the facial nerve for the cure of facial spasm. In a case in which this operation was done for me by Dr. Frazier, paralysis was followed after a time by the return of function without spasm, but later spasm recurred. At one time I had some experiments conducted on animals in the effort to obtain the strength of alcohol which would affect the facial nerve sufficiently to prevent spasm without paralysis, but the work was never completed.

Dr. Temple Fay: In attempting this injection, Dr. Spiller brought out in the Neurological Conference a year ago the possible means of blocking blepharospasm by the injection of alcohol in the branches of the facial nerve. The question came up as to how one could introduce a needle into nerves as fine as the superior and inferior orbicularis branches. It was decided that by using a battery and attaching it to a fine hypodermic needle, it would be possible to search around in the tissues until a direct impulse was transmitted to the orbicularis and the eye was brought into spasm. An injection was made around the nerve fibers thus located and a temporary paralysis of closure of the lids was produced. It was satisfactory. This was just before the meeting in Minneapolis, in 1928. Dr. Williams presented his operation at the Minneapolis meeting and I discussed this case at that time. I received a telegram from Dr. Ornsteen at the meeting saying that the patient was still relieved after fourteen or sixteen days, and then, when I returned, I found that the paralysis was only temporary and that the spasms had returned.

Dr. Alfred Gordon: A young lady, the daughter of a prominent physician, showed the same type of spasm on the left side and fibrillary tremor of the muscles of the face as the patient presented by Dr. Frazier. She was treated with 10 minims (0.6 cc.) of a 40 per cent solution of alcohol. Complete paralysis of the facial nerve developed and lasted for six weeks, after which there was recovery of the movements of the side of the face. For two and one-half years there was absolute relief from the spasm from which she suffered. I have not seen the patient since then.

Dr. A. M. Ornsteen: The operation was undertaken only after the patient was given psychotherapy over a prolonged period of time, which was influential. The psychotherapy was administered with as much careful thought and procedure as was possible. In spite of the negative result, my impression remained that the spasm was of functional character. This is supported further by the observation that the patient has an occupational spasm of the right arm in the form of a writer's cramp. The nature of the spasm did not, however, contraindicate operation and I felt that if the peripheral neuromuscular arc was interrupted there would be a cessation of spasm which would thereby give the patient a symptomatic cure.

The suggestion was made that the basis of the spasm might be a syphilitic disorder of the midbrain. There is not a single sign nor symptom to support this thought. Epidemic encephalitis may manifest itself in this monosymptomatic way and blepharospasm as an oculogyric spasm might be one of the earliest symptoms of the disease. Nevertheless, the patient was presented merely to show the effect of cutting the upper division of the facial nerve for relief from blepharospasm.

A Case of Injury with Compression of the Primary Trunks of the Brachial Plexus Without Sensory Involvement. Dr. Joseph C. Yaskin.

C. A., a negro, aged 39, was admitted to the Graduate Hospital on June 18, 1929, in the service of Dr. Lee, with a gunshot wound in the left upper part of the chest, inability to move the left arm and a slight cough. The wounds of entrance and exit were connected by a line traveling beneath the clavicle through its middle third.

The weakness of the left upper extremity was said to have come on not immediately after but within an hour after the accident. When the patient was seen the next morning, the following neurologic observations were made: The pupils were equal, slightly irregular and responded poorly to light but much better in accommodation. There was no drooping of the eyelids, nor any enophthalmos. All other cranial nerves were normal. Except for disturbance of the left upper extremity and symmetrically exaggerated reflexes in the lower extremities, the neurologic examination gave negative results.

The trapezius and levator anguli scapulae of the left upper extremity functioned normally. There was complete loss of power in the deltoid, becips and triceps, which responded well to direct muscle percussion. There was loss of extension of the wrist and of the fingers but some ability to flex the wrist and the fingers remained. The function of the intrinsic muscles of the left hand was definitely impaired. The biceps and triceps reflexes were entirely lost. There was only slight impairment of touch, pain and temperature sensibility over the ulnar distribution. There was a slightly tender swelling in the supraclavicular fossa. The Wassermann test of the blood gave a 4 plus reaction with all antigens.

On June 20, there was good flexion of the wrist and fingers and good pronation. On June 24, there was considerable return of extension of the wrist and of supination, and sensation appeared normal throughout. On June 26, there was good function of the muscle groups innervated by the median and ulnar nerves. Extension of the fingers and wrist was poor; extension at the elbow was fair. The deltoid, biceps and supinator longus were still without power. On July 1, there was a slight return of function of the flexors of the elbow but not of the deltoid. On July 5, it appeared that the swelling in the supraclavicular fossa, which had been receding, had begun to increase again and a provisional diagnosis of a traumatic aneurysm was made. On July 8, there was a return of power in the flexors of the elbow and some return of function to the deltoid, with fibrillary tremors in the latter.

The patient was given antisyphilitic treatment. The tumor in the supraclavicular fossa continued to increase in size but the motor functions in the upper extremity continued to improve.

At the present time, the only definite abnormalities are weakness and atrophy of the left pectoralis major, deltoid and to a lesser extent of the biceps, supinator longus and triceps. These muscles show fibrillary tremors and diminished idiomuscular responses but no electric reactions of degeneration. The biceps and triceps reflexes are still absent. There are absolutely no sensory changes.

This case presented three interesting aspects: (1) The paralysis was not due to direct injury to the brachial plexus but rather to pressure by the hematoma and to edema in the supraclavicular area, as was suspected by the paralysis coming on within an hour after the injury; this was borne out by the subsequent, almost complete recovery. (2) The recovery occurred early in those parts of the brachial plexus which were farthest away from the supraclavicular swelling, namely, in the muscles supplied by the median and ulnar nerves, that is, the lower primary trunk of the brachial plexus. Next to recover was the group of muscles supplied by the middle primary trunk; that is, the extensors of the fingers, wrist and elbow but not those of the supinator longus. Last to recover, and that less completely, were the muscles supplied by the upper primary trunk of the brachial plexus, that is, the biceps, supinator longus and deltoid. The upper cord lay closest to the aneurysm. (3) The absence of sensory disturbance despite marked motor changes.

DISCUSSION

Dr. Ross H. Thompson: Does Dr. Yaskin think it advisable to attempt to remove the aneurysm by surgical intervention? Two years ago, I examined a man who had the same condition on the opposite side. The aneurysm was of traumatic origin, which caused both motor and sensory symptoms from pressure on the brachial plexus. It was successfully removed by Dr. Ashhurst.

DR. CHARLES H. FRAZIER: Is there any possibility of the motor manifestations being functional? It is difficult to understand why in a compression injury to nerves of mixed function the sensory fibers should escape entirely. If there is any disturbance of function from an injury to a mixed nerve the sensory disturbance usually predominates.

A CASE OF CEREBELLOPONTILE ANGLE TUMOR SHOWING UNUSUAL SYMPTOMATOLOGY. A NEW OPERATIVE APPROACH. DR. ALEXANDER SILVERSTEEN and DR. N. W. WINKELMAN.

Clinical History.—James Mc., a white man, aged 25, referred by Dr. Coombs, was admitted to the Samaritan Hospital on June 21, 1929, in Dr. Bochroch's service. The chief complaints were headache, pain in the left eye, swelling of the gums on the left side and vomiting. Other than a soreness in the left side of the head that he had had for the past two years, the patient was apparently well until two months prior to admission to the hospital, at which time he experienced: severe headache localized on the left side and radiating anteriorly from the temporal region; pain in the left eyeball; impaired vision when looking to the left; swaying on walking; pains in the left ear, with the development of deafness, and an annoying copper-like taste on the left side of the tongue. He vomited once or twice daily for six weeks prior to admission, usually in the morning before eating. The vomitus was coffee colored, thick and contained particles of food eaten on the day before. For four months prior to admission he was an attendant at Byberry.

Examination.—General physical examination gave practically negative results. Repeated examinations of the fundus by Dr. Luther Peter and his staff revealed a neuroretinitis but no papilledema. The fields were normal. The pupils responded to light and in accommodation. The left pupil was smaller than the right. There was a slight recession of the left eyeball and the left palpebral fissure was less than the right. Nystagmoid movements were noted when the eye rotated laterally. Left corneal anesthesia was present with hypesthesia of the left side of the face. There was weakness of the left external rectus muscle. The facial nerve on the left side was not involved, although there was an absence of pain and taste sensation on the left side of the tongue. The lower right side of the face gave evidence of a mild degree of paresis. The vestibular and cochlear divisions of the eighth nerve were involved. A watch tick was heard with the right ear, but not with the left. Tuning forks were heard through the air in the right ear, but not in the left. With an audiometer, the readings were: right ear, 28 per cent; left ear, 0. There were practically no labyrinthine responses. The ninth nerve was not tested. The levator palati was weaker on the left side than on the right.

The pulse was slow in rate, about 45, but of full volume. Laryngologic examination revealed no pathologic changes in the larynx. The grip was equal in the two hands. The finger-to-nose test was well performed. Diadokokinesis tests were well done. The reflexes in the upper extremities were very brisk. No Hoffman's sign was obtained. The abdominal reflexes were present on the left side, but were not obtained on the right. Both patellar reflexes were very prompt. There was a positive Romberg sign. On walking, the patient swayed definitely to the left. When standing, he spread both legs apart. The ataxia was present whether the eyes were open or closed. The heel-to-knee test showed marked incoordination on both sides. The patient showed no evidence of any sensory disturbance.

Diagnosis.—A diagnosis of a left cerebellopontile angle neoplasm was made.

Course.—The temperature from June 21 to July 15 varied from normal to subnormal. The pulse rate was significant, varying from 48 to 44. Laboratory studies gave negative results. Roentgen examination of the skull gave negative results. During this time the patient's condition became progressively worse. He complained of severe pain in the left temporal region, and pain in the left eye; at times the pain was felt in both eyes. He also seemed to be greatly annoyed by a coppery taste on the left side of the tongue. Projectile vomiting increased greatly in frequency. He was drowsy and apathetic, and his disposition became rather pugnacious and disagreeable.

The patient was referred to Dr. W. Wayne Babcock for an operation, which was performed on July 16. The usual suboccipital route was employed. A thick-walled cyst, about the size of a cherry, was visible anteriorly; it was adherent to the nerve trunks in the left cerebellopontile angle. The cyst was opened and evacuated. Owing to the nerve connections, a minute portion of the cyst was removed, leaving an opening 5 mm. in diameter.

Postoperatively, the patient seemed somewhat improved. Headache and projectile vomiting were less frequent than before the operation. He showed marked mental changes, however, in that he became obstreporous and difficult to control, at times becoming maniacal. Later, he seemed to be improved and requested to leave the hospital; he was discharged on August 5. The neurologic observations at this time were practically the same as those prior to the operation.

While at home, at first he managed to walk by supporting himself with the aid of chairs, etc. Soon he became progressively worse. Projectile vomiting increased in severity and frequency and in about the third week he was unable to take any water without vomiting. At this time he practically lost the use of the right arm and right leg. He could not hold objects in the right hand.

Second Admission.—On September 12, he was readmitted to the Samaritan Hospital on the service of Dr. Winkelman. He complained of severe pain in the left side of the face and pain in the left eyeball and inner side of the left cheek. The patient indicated that the pain was distributed along the course of the three divisions of the trigeminal. The pain apparently was continuous in character, with paroxysms of increased intensity in which the patient would cry out and scream. The general physical condition was poor. Projectile vomiting was virtually continuous.

Neurologic examination at this time revealed the following conditions: Optic nerve: On September 15, a fundus examination by Dr. Gouterman showed in the left eye, 3 diopters, in the right eye, 2.5 diopters of swelling. The pupil of the left eye was smaller than that of the right; there was recession of the left eyeball. The palpebral fissure of the left eye was less than that of the right. Corneal anesthesia of the left eye was present with hypesthesia of the left side of the face.

There was a slight tendency of the jaw to deviate to the left. Weakness of the left external rectus was present. The facial nerve on the left side was apparently not involved. There was marked paresis of the lower quadrant of the face on the right side. An eighth nerve involvement was present as on the previous examination. A second Bárány test again gave labyrinthine reactions. Other cranial nerves were not affected. The finger-to-nose and finger-to-finger tests showed slight incoordination of the left side. Diadokokinesis tests were well performed. The patient was able to raise the right upper extremity only a few inches from the bed. There was practically no grip in the right hand. The reflexes in both upper extremities were very brisk. A suggestive Hoffman sign was present in the right hand. Both patellar reflexes were markedly plus, more so on the right. A positive Babinski sign was present in the right foot. The heel-to-knee test demonstrated marked incoordination in both lower extremities.

From the foregoing observations, Dr. Winkelman made a diagnosis of a refilling of the cyst with extension of the lesion forward and anteriorly reaching high up on the pons. He suggested operation and particularly indicated that, owing to the high location of the lesion, the approach should be made more anteriorly and not through the usual posterior route.

On September 19, an operation was performed by Dr. Temple Fay, and following is a résumé of his operative notes:

A subtemporal decompression was made on the left and full exposure obtained at the left temporal lobe. The dura was then opened and the temporal lobe elevated. One of the large venous sinuses emptying into the lateral sinus was ligated. The hemisphere was then elevated and the tentorial surface was easily seen. At the apex of the tentorial surface a bulging mass, the size of an olive, was seen beneath the tentorium. An incision was made through the tentorium and the tumor was thus encountered; it was soft and gelatinous, and some of the

mass was removed by a curet and much of it by suction. After removal of the tumor mass, it was noted that there was a large cyst under the tentorium, closely approximating the crus and upper pons. This cyst was opened and evacuated. Dr. Fay stated that although the technical difficulties are greater, the value of this approach in certain cases is to be considered superior to the usual posterior fossa approach.

Pathologic Diagnosis (Dr. Winkelman).—The diagnosis was: perineurofibroblastoma.

The patient reacted well from the operation, but it was evident that he had a jargon aphasia which was marked by inability to enunciate words or make himself understood. On September 25, six days after the operation, he began to show return of speech, but there was still a definite motor and sensory aphasia. During this time, he also became restless and noisy, and on two occasions tore off the dressings requiring, in one instance, suturing of the scalp. From this time on the patient progressively improved, the aphasic symptoms becoming less evident. Motor aphasia was the first to disappear, alexia next and lastly word deafness.

A final examination on October 10 resulted as follows: There was no evidence of aphasia. Nystagmoid movements were few and occasional when the eyes were rotated to extreme horizontal planes. Fifth nerve sensory and motor involvement was still evident. A mild weakness of the left external rectus was still present. Horner's syndrome was not present. The lower quadrant of the right side of the face still showed mild paresis. The eighth nerve showed no change. There was no weakness of the upper extremities, although a Hoffman sign was occasionally obtained in the right hand. Both patellar reflexes were exaggerated, the right more than the left. Clonus and Babinski signs were not obtained.

The patient's only complaint since the second operation has been pain in the left side of the face, which is becoming less. At times one gets the impression that it is a paresthesia rather than pain.

Summary.—The features in this case are: 1. The complaint of trigeminal neuralgia as an outstanding symptom in association with other angle symptoms; neuralgia seems to occur rarely in lesions in this location. (Krause, Lexer, Weisenburg and Parker reported cases of cerebellopontile angle tumors in which the symptoms were mistaken for tic douloureux.) 2. The presence of a Horner's syndrome which disappeared after the second operation. 3. Postoperative aphasia with rapid recovery. 4. The accurate localization and the new method of approach in operating in this case by Dr. Temple Fay.

DISCUSSION

Dr. N. W. Winkelman: This patient presents symptoms that are uncommon in a tumor of the eighth nerve. Pathologically, the tumor was characteristic of a tumor growing from the sheath of the eighth nerve, a perineural fibroblastoma. The symptoms were: complete contralateral hemiplegia, including the lower part of the face, and severe pain in the distribution of the fifth nerve. For these reasons, I thought that the tumor was higher than the usual angle lesion. In discussing this with Dr. Fay I told him my suspicions, but left the technic to him. As a result of the operation, the patient had temporary symptoms of involvement of the left temporal lobe as the result of trauma.

I think that the operation performed in this case is excellent for a right-sided lesion, but in a right-handed person there is danger of permanent sensory aphasia.

Dr. Temple Fay: The operative approach here was practically a left temporal craniotomy. The patient had a high degree of choking of the disks (intense intracranial pressure) and for that reason I did a decompression. It was not known whether one would be able to reach the tumor owing to the patient's poor condition. There was very little time in which to do the procedure of choice — an osteoplastic flap. I thought I saw the necessity of relieving him by decompression in case the tumor was inoperable.

Dr. Babcock did a Cushing cross-bow exploration of the posterior fossa. It was impossible to reach the tumor through the approach that had been previously used, and as Dr. Winkelman pointed out, this lesion was above the angle. By lifting up the left temporal lobe a tumor mass was seen bulging through the tentorium; I was able to incise the tentorium and scoop out the tumor with the aid of an electrocautery. The facial nerve was retracted and the two ends of the fusiform tumor were cut. Behind the tumor mass and up against the crus was a peanut-shaped cyst; it extended through the incisura of the tentorium so that it was necessary to section the incisura, which I did. The tumor was under and extended through the crus. This gave easy removal and a nice exposure. I did not expect the patient to recover. I eliminated the pressure phase. I would have used a different technic if the patient's poor condition had not interfered and would have devised a cranioplastic flap and left no decompression.

Dr. Charles H. Frazier: In regard to the association of trigeminal neuralgia with angle tumors, many of you will remember an extraordinary case reported by Dr. Weisenburg. For a number of years this patient complained of pain and paresthesia in the trigeminal zone. He had been subjected to many operations, both central and peripheral, at many hands. At no time were there any other symptoms to suggest an angle tumor. Without warning, he suddenly became unconscious and died within a few hours. At autopsy a neurofibroma of the acoustic nerve was found. In the case reported by Dr. Fay there was a hemiparesis; this reminded me of the series of cases from Adson's clinic which were reported at a recent meeting of the American Neurological Association. In this series of posterior fossa tumors the hemiparesis was found, by microscopic study, to be due to pressure on the crus.

As I listened to the account of the first operation in the patient of Dr. Fay, it seemed apparent that the cyst observed by the operator was one such as one sees not uncommonly in advance of angle tumors. The association of cysts in this relation with angle tumors is not infrequent.

It is not clear to me how, as Dr. Winkelman assumes, there can be any variation in the location of an acoustic tumor, since these tumors take origin from the acoustic nerve as it enters the internal auditory meatus. The point of origin being constant, it is difficult to picture some as occupying a high and some a low position as Dr. Winkelman would have us believe. The difference in the clinical picture is due to variation in size rather than to position.

This is not the place to discuss problems in technic, but I may remind you that Dr. Naffziger of San Francisco used the transtentorial approach several years ago; we have used it in the neurosurgical clinic at the University Hospital. As a matter of fact, this approach was suggested as long ago as 1893. Wholly apart from its origin, I am not at all convinced that this approach will ever be accepted as preferable to the conventional approach through the posterior fossa.

Dr. N. W. Winkelman: As one looks at specimens of angle tumors, one is struck by the fact that tumors at times are located low and involve the medulla more than the pons and at times the pons more than the medulla. Many times the fifth nerve is compressed, but it is rare for the peduncle to be involved. Many times, the tumor is much below the fifth nerve. I grant that these tumors grow from the sheath of the eighth nerve but there can be growth mainly above or growth mainly below. What determines the pain I do not know, since it is rare and yet the lesion often touches the fifth nerve. In this case I thought that with the pain and with the involvement of the face in the hemiplegia, I was safe in my localization.

Narcolepsy. Dr. Max Levin.

This article appeared in full in the December issue of the Archives **22**:1172, 1929.

Radiogenic Microcephaly: A Survey of Nineteen Recorded Cases with Especial Reference to Ophthalmic Defects. Dr. Leopold Goldstein.

This article will be published in full in a later issue of the Archives.

Book Reviews

DARK ADAPTATION. A REVIEW OF THE LITERATURE. By DOROTHY ADAMS. Special Report 127 Medical Research Council. Price, 5 shillings. Pp. 138. London: His Majesty's Stationery Office.

The British Medical Research Council, in publishing the reports of the committee on the physiology of vision, has just issued Special Report Series 127. It is a most uncommon work from that standpoint only for which it is presented, i.e., a review of the literature. The author has considered the subject from every possible angle and, as a result, has presented a complete reference book of inestimable value.

The book is subdivided into sixteen sections, each covering some general subheading of the subject. Within each section she explains the problem peculiar to it. She immediately follows this with the names and dates of the various investigators and observers who have written relative to that topic and then describes in adequate abstract their work and conclusions. Instead of the chaos which might arise in such a compilation, a surprisingly coherent and readable text has been developed. Quoting the preface, in part, ". . . it is issued in the hope that it may assist workers in this field to have ready access to the work already done in the subject, published as it has been through channels of many different kinds and in various countries." The report certainly fulfils this hope.

The first two sections deal with the dark adaptation of chromatic and achromatic light stimuli. The next three sections discuss regional variations in the sensitivity of the dark-adapted retina, dark adaptation at the fovea and visual acuity and dark adaptation. These first five sections are well explained, in addition to the text matter, by many charts and plotted curves. Section six considers the difference threshold in relation to dark adaptation. This is a section on the subject of the discrimination of differences of brightness. Section seven describes the various factors which cause individual variations in dark adaptation. Sections eight and nine consider scotopic vision. The first of these deals with scotopic vision in relation to the stimulus; the second with certain subjective characteristics of scotopic vision as: its luminosity curve, the Purkinje phenomenon, color matching, the blue sensation of the rods and after-image phenomena. Section ten discusses the variations of dark adaptation as they exist in such pathologic conditions as color blindness, night-blindness and other conditions of the eye. Section eleven is an interesting section on dark adaptation in vertebrate and invertebrate animals. Section twelve explains the structural changes in the retina and the pupil which accompany adaptation. Section thirteen describes the chemistry of the retina and the chemistry of visual purple. Sections fourteen and fifteen discuss the electrical responses of the dark-adapted retina, and the responses to stimulation of the eyeball by electrical stimuli, the roentgen rays and pressure stimuli. Section sixteen, the last of the subheadings, deals wholly with the various theories of dark adaptation as they apply to the photo-electrical considerata of retinal sensitivity, to the course of dark adaptation, dark adaptation at the fovea, the early part of dark adaptation, the change from rod to cone mechanism, the relationship of visual purple to dark adaptation, the individual functions of the various retinal elements and the relationship of dark adaptation to nerve reaction.

A glance through the list of references shows these as ranging from a work of Bouguer in 1760, on intensity of illumination, up through to the work of Lasareff in 1926, and the work of Parsons and Ferree and Rand in 1927. Their scope (the references) is as all embracing as the time intervals: Aubert's repeated discussions on the sensitivity of the retina; Broca's experiments on the visual sense and the light sense; von Hess' studies, extending over a period of more

than thirty-three years, on the physiology of vision; Uhthoff's early work on visual acuity and luminosity intensity, etc. The fact that this list includes 846 separate references makes any further explanation of it wholly superfluous.

CONTRIBUTIONS TO PSYCHIATRY, NEUROLOGY AND SOCIOLOGY. Dedicated to the late Sir Frederick Mott, K.B.E., LL.D., M.D., F.R.C.P., F.R.S. Edited by J. R. Lord, C.B.E., M.D., F.R.C.P.E. on behalf of the Mott Memorial Committee of the Royal Medico-Psychological Association, with an appreciation by W. D. Halliburton, M.D., F.R.C.P., F.R.S. Cloth. Price, 21 shillings. Pp. 401, with numerous plates and illustrations. London: H. K. Lewis & Co., Ltd., 1929.

Sir Frederick Mott was the seventy-seventh president of the Royal Medico-Psychological Association at the time of his death on June 8, 1926. This book, containing contributions from colleagues, friends and former pupils, is an expression of the high esteem in which he was held by all who knew him. The introductory pages contain a poem in memoriam, some biographic notes and a preface outlining the development of the book. The main body of the book contains thirty-one articles covering a wide range of subjects, indicative of the broad interests of Sir Frederick Mott, many of the authors stating that the work was inspired by some association with him. These articles are all of a high degree of excellence, and many of them are by men who are recognized leaders in their respective fields. The collection is of interest to every neurologist and psychiatrist, and the book should be in every library devoted to such topics.

The articles are : 1. Frederick Walker Mott: Some Personal Reminiscences, by W. D. Halliburton. 2. Some Common Errors in Neurological Nomenclature, by Sir E. Sharpey-Schafer, of Edinburgh. 3. The Prevention and Early Treatment of Mental Disorders, by Sir Hubert Bond, of London. 4. The Nervous System of Mammalia Without Cerebellum, by C. Winkler, of Utrecht, Holland. 5. Mind, Religion and Medicine, by Frederick Peterson, of New York. 6. An Isometric Study of the Human Knee and Ankle Reflexes, by F. Golla and L. C. Cook, of the Maudsley Hospital, London. 7. The Variations in the Folding of the Visual Cortex in Man, by G. Elliott Smith, of London. 8. The Rôle of Mental Confusion in Prognosis, by Joseph Shaw Bolton, of Leeds. 9. Mental Disorder and Its Relation to Deficient Oxidation in the Brain Tissue, by F. A. Pickworth, of Birmingham. 10. The Relationship of Mental Deficiency to Mental Disease in General, by A. F. Tredgold, of London. 11. A Plea for Accuracy in the Assessment of Alcoholic Morbidity, by Edward Mapother, of London. 12. On the Innervation of the Gallbladder, with Special Reference to the Ganglion Cells, by T. Morowoka, of Kyushu, Japan. 13. Sir Frederick Mott and the Society of English Singers and Phonological Science, by W. A. Aikin, of London. 14. The Provision of Early Treatment for Nervous and Borderland Patients, by A. Helen Boyle, of Brighton, Eng. 15. 15. A Study of the Depressive Reaction, by W. S. Dawson, of Sidney, N.S.W. 16. Vision and Colour-Vision, by F. W. Edridge-Green, London. 17. Observations upon the Histopathology of General Paralysis Treated with Malaria and Relapsing Fever, by C. Geary, of Maudsley Hospital, London. 18. The Aetiology of Alcoholism, by Bernard Hart, of London. 19. Ibsen, the Apostle of the Psychopath, by Smith Ely Jelliffe, of New York. 20. Aperçu de la thérapie des maladies nerveuses et mentales et de son état actuel (in French), by C. U. Ariëns Kappers, of Amsterdam. 21. The Ocular Syndrome of Epidemic Encephalitis, by P. K. McCowan and L. C. Cook of the London County Mental Hospitals. 22. Further Blood-Sugar Studies in Mental Disorders, by S. A. Mann and F. L. Scott, of the London County Mental Hospitals. 23. Some Settled and Unsettled Problems in Neurosyphilis, by G. H. Monrad-Krohn, of Oslo. 24. Ricerche chimiche ed istologiche sul nevrasse di cani tiroidectomizzati (in Italian), by Giacomo Pighini, of Rome. 25. Ueber Vershiedenheiten in der geographischen Verbreitung der Paralyse (in German), by Felix Plaut, of Munich. 26. The Incidence of Digestive Alkaluria in Normal and Psychotic Subjects, by

Isabella Robertson, of the London County Mental Hospitals. 27. Un cas de tumeur du bulbe à symptomatologie cortico-pariétale (avec quelques considerations sur la valeur pathogénique des troubles dissociés de la sensibilité), by G. Roussy and Gabrielle Levy, of Paris. 28. Some Factors Related to the Immediate Future of the General Paralytic Treated with Malaria, by G. de M. Rudolf, of Claybury Hospital. 29. The Conditioned Psycho-Galvanic Response, by David Slight, of Montreal. 30. Remarks on the Diagnosis of the Paranoid Type of Syphilitic Psychosis ("Syphilitic Hallucinosis" of Plaut), by August Wimmer, of Copenhagen. 31. Sir Frederick Mott, K.B.E.: His Life and Work, by C. von Monakow, of Zurich.

In a final article is presented a list of the writings of Sir Frederick Mott, which include eleven books, eight articles in various treatises, twelve public lectures, and 181 papers in various journals.

THE NEUROSES. By ISRAEL S. WECHSLER. Price, $4. Pp. 330. Philadelphia: W. B. Saunders Company, 1929.

In this book the author consistently adheres to the psychologic approach in the study and treatment of the neuroses. The main part of the book is devoted to the presentation of the freudian point of view and the psychoanalytic method of treatment. While in the discussion he presents other points of view, he does so only to tear them down and to show the virtue of the psychoanalytic method. His classification of the neuroses is that of Freud. The clinical manifestations bear the same stamp and, in the discussion of the diagnosis, course, prognosis and treatment, he again emphasizes the psychoanalytic method, although he does mention other methods. He has not much use for the removal of focal infections, glandular treatment, rest cures, suggestion, hypnotism or persuasion. While he admits that the psychoanalytic approach cannot be used in every form of neurosis, and does no good in most, nevertheless, in the illustrative examples that he uses, the psychoanalytic method is the only one that presents any lasting results.

He gives only a summary of the method to be adopted in psychoanalysis and emphasizes the fact that to practice psychoanalysis one must be well trained and properly qualified.

While the reviewer has no quarrel with the author in the fact that a psychologic approach both in the understanding and treatment of the neuroses is distinctly the best, nevertheless the general practitioner or student, for whom the book is written, will necessarily come to the conclusion, after reading it, that he is not only unqualified but that he is unfit to treat a neurotic patient, and that the thing for him to do is to turn his patient over to a psychoanalyst.

THE LAYMAN LOOKS AT DOCTORS. By S. W. and J. T. PIERCE. Pp. 251. New York: Harcourt, Brace & Company, 1929.

This book deals with a long and stubborn case of neurasthenia with suicidal tendencies in a patient who had, apparently, an entirely happy background. The introduction and conclusion were written by the patient's husband, while the rest of the book was written by the patient herself. Each chapter describes a different method of treatment under different physicians, neurologists, neuropsychiatrists, psychiatrists, an endocrinologist, a diagnostician, and others. After more than four years the patient was permanently cured by treatment with psychoanalysis. The chapter headings are as follows: Treatment by Minimization, Treatment by Methodic Brutality, Treatment by Encouragement and Infinite Patience, Treatment by Sex Appeal, Treatment by Terminology, Treatment by Experimentation, Treatment by Efficiency, Treatment by "Common Sense."

The book is of interest to neurologists in so far as the thoughts going on in such a patient's mind are clearly shown. It seems, however, to be more a criticism of the personality of each physician who treated the patient than of the general method of treatment employed.

ÉTUDES NEUROLOGIQUES. Third Edition. By GEORGES GUILLAIN. Price, 70 francs. Pp. 448. Paris: Masson & Cie, 1929.

This volume represents the third of a series of collected reprints appearing under the leadership of Professor Guillain and his associates from the neurologic wards of the Salpêtrière. Altogether there are twenty-three articles, which are divided under the following headings: (1) cerebral tumors; (2) pathology of encephalitis; (3) pathology of the crus, pons, medulla and spinal cord; (4) spinal cord diseases; (5) pathology of the cranial nerves and roots; (6) muscular atrophies; (7) miscellaneous articles and (8) history of neurology, particularly that of Duchenne.

It compares favorably with the two previous volumes which have been reviewed in this journal. It is impossible to comment on all these articles individually, which were published originally in the current French literature. Most of them have already been abstracted in the ARCHIVES. These articles, however, furnish an excellent survey of modern French neurology which compares favorably with the work of any other country.

EPIDEMIC ENCEPHALITIS. Etiology. Epidemiology. Treatment. Report of a Survey by the Matheson Commission. Pp. 849. New York: Columbia University Press, 1929.

One of the encouraging things about the problem of encephalitis is the fact that throughout the world many efforts are being made to solve the question of its etiology and treatment. Largely due to the generosity of Dr. William John Matheson, an intensive research is being conducted in New York. One of the first things that this research has done has been to collect and tabulate what is known and what is being done for this disease. This survey consists of about 850 pages, half of which are taken up by the bibliography. The subject matter itself is divided into: (1) Summary of Investigations on the Etiology of Epidemic Encephalitis; (2) Other Types of Encephalitis, Including Post-Vaccinal Encephalitis; (3) Summary of the Treatment of Epidemic Encephalitis; (4) Epidemiology.

The work was done under the direction of Dr. Josephine B. Neal, and presents an excellent summary with comments on what is known of this disease.

SHELL SHOCK AND ITS AFTERMATH. By NORMAN FENTON, PH.D. With an Introduction by Thomas W. Salmon, M.D. Illustrated. Price, $3. Pp. 167. St. Louis: The C. V. Mosby Company, 1929.

This book presents and follows through an interesting idea. Dr. Fenton was one of the psychologists in Base Hospital 117, which was the only hospital for patients with shell-shock conducted by the American forces in France. He conceived the idea of following up 3,000 cases, so as to see what happened to the patients after they returned home and tried to readjust themselves to civilian life. His results show that, to begin with, the Armistice did not bring about spontaneous cures, nor did it have a great influence in curing symptoms. It also showed that the subsequent course of these patients is no different from that of psychoneurotic patients in civilian life. The work was excellently done and is well worth while; it is especially interesting to the many neurologists who were concerned in the treatment of such patients during the war.

AN INTRODUCTION TO THE STUDY OF THE NERVOUS SYSTEM. By E. E. HEWER, D.Sc., and G. M. SANDES, M.B., B.S., M.R.C.S., L.R.C.P. Price, $6.50. Pp. 98. St. Louis: C. V. Mosby Company, 1929.

In a book of ninety-eight pages the authors have produced some of the best illustrations in any textbook on neurology. The book consists of two parts: the first is full of colored illustrations which show beautifully, for example, the diagram of the path of the fifth nerve; a new illustration of the fibers of the internal capsule;

the central connections of all the cranial nerves, etc. In the second part, which is physiologic, a short summary is given of the functions of the different parts of the brain.

There is no doubt that the authors have fulfilled what they set out to do; that is, produced a book which helps the student and illustrates those points which are not usually found in the average textbook.

DIE VORDER- UND MITTELHIRNGANGLIEN DES MENSCHEN ALS PLASTISCHE GEBILDE. By BENNO SCHLESINGER, Demonstrator of Anatomy in the University of Wien. Price, 6.60 marks. Pp. 55, with 14 text pictures and 10 stereophotographs. Berlin: Julius Springer, 1928.

This article appeared in the *Zeitschrift für die gesamte Neurologie und Psychiatrie* and is now published in a small monograph. A new method for studying the gray masses within the substance of the brain and in the mesencephalon is given. It seeks to correct the old method of trying to learn the anatomic relations by piecing together cross-section after cross-section. It differs in no great essential from the method employed by Meyer and Hausman in the general study of the brain by reconstructing it in model form. The method described in this little pamphlet is valuable for teachers of anatomy for graduate students. It is obviously too complicated for undergraduate teaching.

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